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OCULAR SIGNS OF INTRACRANIAL SACCULAR ANEURYSMS

EXPERIMENTAL WORK ON COLLATERAL CIRCULATION THROUGH THE OPHTHALMIC ARTERY

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This paper was written with the purpose of reviewing the present state of knowledge on the ocular signs of saccular aneurysms at the base of the brain. It is divided into three parts. Part 1 illustrates the topical diagnosis from the standpoint of ocular signs. This has already been treated by Jefferson,[1] whose paper, which appeared in 1937, was largely based on his own cases but also reviewed cases in the literature. Part 1 of the present paper does not contain new material but is included for its intrinsic interest. Part II contains a description of ocular signs which, so far as we are aware, have not hitherto been associated with intracranial aneurysms. The most important of these signs, abnormalities of ocular movement and pupillary changes, are caused by misdirection of regenerated third nerve fibers. An additional abnormal lid movement and pupillary phenomenon are recorded, both of which are dependent on sensitization to chemicals mediated by the autonomic nervous system. Part III is based on experimental work which demonstrates some features of the collateral circulation of the ophthalmic artery. The experiments, some of which were performed by Elschnig[2] in the early 1890's, illustrate the free anastomosis between the branches of the

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1. Jefferson, G.: Compression of the Chiasma, Optic Nerves and Optic Tracts by Intracranial Aneurysms, Brain **60**:444-497, 1937.

2. Elschnig, A.: Ueber den Einfluss des Verschlusses der Arteria ophthalmica und der Carotis auf das Sehorgan, Arch. f. Ophth. (pt. 4) **39**:151-177, 1893.

external carotid and the ophthalmic artery. Birley and Trotter [3] quoted Elschnig's experiments in a paper in which they described the results following ligation of the great vessels of the neck. We repeated Elschnig's experiments and added others of our own in order to demonstrate experimentally a fact which Dandy [4] has proved clinically in cases in which he has performed his "trap" operation: that ligation of the internal carotid, doubly, in the neck and intracranially in front of the cavernous sinus, isolates the ophthalmic artery and rarely causes blindness homolaterally.

A brief review of the relevant anatomy and pathology is given as an approach to the subject.

ANATOMY

The circle of Willis, roughly hexagonal in shape, is formed by a continuous series of vessels at the base of the brain connecting both the homolateral and the contralateral anterior, middle and posterior cerebral arteries. The forepart of the circle is formed by the anterior cerebral arteries connected by the broad, short anterior communicating artery. The centrolateral boundary on each side is formed by the posterior communicating artery, which establishes connection between the carotid and the posterior cerebral artery. The posterolateral boundary is formed by the posterior cerebral artery, which on each side arises from the basilar artery and serves to connect the internal carotid system with the basilar-vertebral system. Variations in the arterial circle are commonly observed, and this is particularly true in cases in which aneurysm is present. The posterior communicating artery occasionally replaces the posterior cerebral artery. The upper part of the internal carotid artery may be missing, and the posterior communicating artery, springing from the posterior cerebral artery, may become the middle cerebral artery. The ophthalmic artery, usually pictured as arising from the carotid artery outside the cavernous sinus, often, according to our experience, arises from this vessel within the sinus. Occasionally the ophthalmic artery is replaced by a branch from the middle meningeal artery (Cunningham).

The relationship of the arteries, optic nerves, chiasm and nerves at the base of the skull is shown diagrammatically in figure 1.

Jefferson pointed out that anteriorly the arterial system lies superiorly to the visual system, whereas posteriorly this relationship is reversed.

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3. Birley, J. L., and Trotter, W.: Traumatic Aneurysm of the Intracranial Portion of the Internal Carotid Artery: Note on Effects of Obstruction of the Carotid Circulation on the Homolateral Eye, Brain **51**:184-208, 1928.

4. Dandy, W. E.: Intracranial Aneurysm of the Internal Carotid Artery Cured by Operation, Ann. Surg. **107**:654-659, 1938; Treatment of Internal Carotid Aneurysm Within the Cavernous Sinus and Cranial Chamber, ibid. **109**:689-711, 1939.

PATHOLOGY

Intracranial aneurysms may be divided into two large groups: (1) arteriovenous aneurysms, which in turn may be divided into (*a*) fistulas between the internal carotid artery and the cavernous sinus and (*b*) cirsoid aneurysms, and (2) a subgroup consisting of (*a*) saccular aneurysms and (*b*) fusiform aneurysms. This paper deals only with the second group.

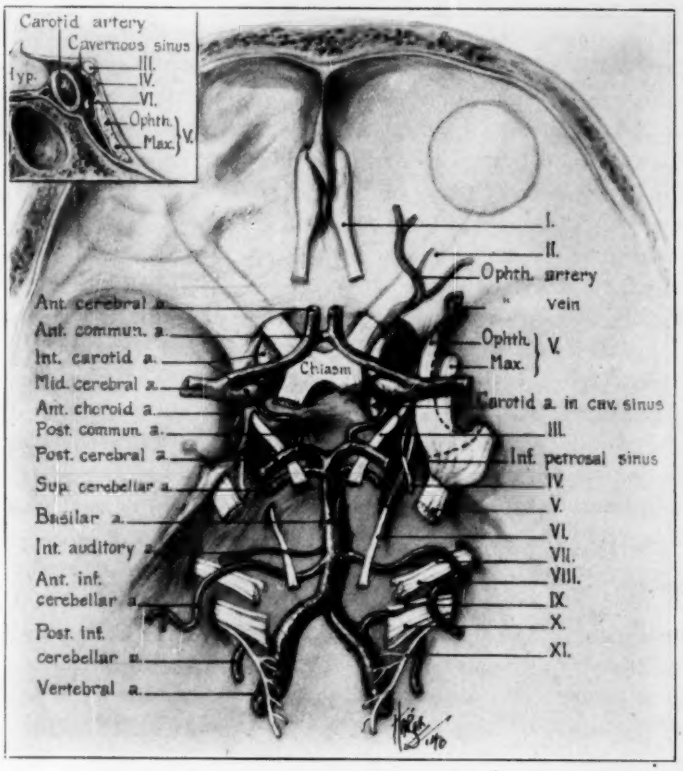

Fig. 1.—Composite drawing of the regional anatomy of the base of the skull, cranial nerves, circles of Willis and cavernous sinus.

Saccular aneurysms can be classified etiologically as follows: 1. Miliary aneurysms, which are situated in the walls of smaller vessels, usually in the substance of the brain. These aneurysms arise as a result of atheromatous changes in older persons and as a result of rupture may account for apoplexy. Their presence cannot be detected prior to rupture. 2. Mycotic aneurysms, which arise through the deposition of septic emboli in the walls of the arteries. They occur not uncommonly in the vessels of the circle but also occur in any of the other cerebral

arteries. Persons who present signs of aneurysm and who are known to have bacterial endocarditis or other septic involvement should be suspected of having this type of vascular disease. 3. Post-traumatic aneurysms. 4. Atheromatous aneurysms in the circle. 5. Congenital, or "berry," aneurysms. These are thought to arise as a result of congenital deficiency in the walls of the cerebral vessels at their bifurcations. They are often confined to the circle of Willis but may be found on the larger cortical arteries or on the middle meningeal artery. With the exception of miliary aneurysms, these are of more frequent occurrence than any other type. Since congenital aneurysms do not usually account for symptoms until adult life has been reached, their designation as "congenital" requires explanation. Forbus [5] pointed out that in the earlier stages of development when the larger cerebral vessels have attained a muscular coat their branches are represented only by tubes of epithelium. At the point of union of the parent vessel and its branches there is every likelihood of a defect because of the change in thickness of the walls of the two arteries. Congenital aneurysms are usually seen, therefore, in the union, or "crotch," between the larger vessels and their branches. Occasionally they arise from the main stem. Usually they are small—hence their description as "berry" aneurysms—and several such aneurysms may be present in one person. Rarely do they attain the size of 8 to 10 cm., and when they do they are almost always attached either to the common carotid or to the basilar artery (Matas). There is considerable variation in size and in thickness of the aneurysmal wall. Pulsation may be detected during life in some cases but is absent when there is a thick wall and the lumen is partially filled with clotted blood. These aneurysms are commonly attached to adjacent structures, the optic nerves, the chiasm and the oculomotor and abducens nerves; occasionally they may be embedded in the floor of the third ventricle. Serial sections of the aneurysmal wall reveal narrowing or even absence of the muscularis. A site of previous rupture and consequent "leak" may be identified by the presence of fibrous tissue filling the defect. Rupture of such aneurysms is one of the common causes of sudden death. The site of occurrence varies in individual series. Dott [6] said that the commonest site is in relation to the termination of the internal carotid artery on the left side.

Congenital aneurysms rarely are associated with signs of other diseases. Fearnsides, among others, emphasized that syphilis plays no part in their development. While vascular hypertension does not predispose to them, slight elevations of blood pressure may cause rupture. Coarcta-

5. Forbus, W. D.: On the Origin of Miliary Aneurysms of Superficial Cerebral Arteries, Bull. Johns Hopkins Hosp. **47**:239-284, 1930.

6. Dott, N. M.: Intracranial Aneurysms: Cerebral Arterio-Radiography: Surgical Treatment, Edinburgh M. J. **40**:219-240, 1933.

tion of the aorta is frequently associated with congenital aneurysm, as has been described by Baker and Shelden.[7] We have observed 2 cases, in one of which there were clinical symptoms of coarctation as well as neurologic signs due to aneurysm. In the other the aneurysms were observed at postmortem examination. There are two possibilities: (1) the aneurysms in such cases may arise from the increased pressure in the cerebral vessels due to the aortic stenosis or (2) both the aneurysms and the coarctation may be expressions of congenital anomalies of the blood vessels.

PART I. THE TOPICAL DIAGNOSIS OF SACCULAR ANEURYSMS

It is remarkable that the usual perspicacity of the earlier clinicians in correlating clinical signs and postmortem observations was not evidenced in the case of aneurysms of the cerebral vessels other than those of the arteriovenous type. Symonds[8] in the early 1920's placed the clinical diagnosis of intracranial saccular aneurysms on a sound basis. He described the cardinal points in diagnosis: (1) neighborhood signs, such as paralysis of the oculomotor nerve and pressure on the optic nerves, the chiasm or the tracts; (2) the presence of subarachnoid hemorrhage; (3) signs of disease which might produce an aneurysm, these being absent in the case of congenital aneurysms (in a person suffering either from infective endocarditis or from arteriosclerosis and having signs suggesting basilar involvement, aneurysm is always a probability), and (4) a history indicating previous subarachnoid hemorrhage together with signs of tumor at the base of the brain.

The ocular signs important in the diagnosis are generally well known. Pain of sudden onset in or about the eyes is probably the most frequent symptom of an aneurysm, and it is a neighborhood sign. It usually affects the eye and the homolateral frontal region but may not be so sharply localized. The pain often is excruciating; usually it is intermittent but it may be constant. Pain may recur for days or weeks before there is any evidence of paralysis of the oculomotor nerve, and indeed such paralysis may never develop. Corneal anesthesia may be present, particularly in cases of aneurysm arising within the cavernous sinus (Jefferson), but pronounced anesthesia was not present in any of our cases.

Paralysis of the oculomotor nerve in varying degrees may follow within hours, days or weeks after the commencement of pain. Ptosis and some degree of internal ophthalmoplegia are usually present when the aneurysm is situated at the anterior end of the circle of Willis.

7. Baker, T. W., and Shelden, W. D.: Coarctation of the Aorta with Intermittent Leakage of a Congenital Cerebral Aneurysm, Am. J. M. Sc. **191**:626-633, 1936.

8. Symonds, C. P.: Spontaneous Subarachnoid Haemorrhage, Quart. J. Med. **18**:93-122, 1924.

Paresis of the abducens nerve, unilateral or bilateral, is seen when the aneurysm is situated posterior to the middle cerebral artery. Retinal hemorrhage, often subhyaloid, is present in a minority of cases in our experience. This does not conform to the experience of Wagener and Foster,[9] who, however, were describing only ruptured intracranial aneurysms seen at the time of subarachnoid hemorrhage. In 1 case we observed massive subhyaloid hemorrhages confined to one eye. Papilledema is in some instances associated with subarachnoid hemorrhages. It may also be observed as a result of a posteriorly situated aneurysm, which may produce symptoms entirely similar to those of neoplasm. Exophthalmos has been relatively uncommon in our experience but was present in 2 of 3 cases of intracavernous aneurysms.

The topical diagnostic value of field defects (or the absence of such defects) merits further description. As already stated, our observations conform to those of Jefferson, whose manner of systematic description we have attempted to follow. It is of some interest that in our cases, here summarized, the presence of aneurysm has been verified either at operation or at autopsy in all but 2 cases. Visual field defects discovered in patients observed in the Johns Hopkins Hospital and in the Baltimore City Hospitals are described hereafter.

Aneurysms Accounting for Unilateral Defects in Vision.—The relationship between the carotid artery and its terminal branches and the optic nerve suggests that unilateral visual defects as a result of an aneurysm in this region might be anticipated. Such aneurysms, which Jefferson described as anterior and supraclinoid, frequently produce homolateral loss of vision which varies between minimal diminution and complete blindness, small aneurysms often producing no visual defect. Junction scotomas, as described by Traquair and accounting for homolateral hemianopic paracentral defects, may be produced by an aneurysm in this vicinity. In some instances there is an associated temporal scotoma in the visual field of the opposite eye. We have observed total loss of vision on the side of the aneurysm with retention of normal vision in the opposite eye. We have also seen partial loss of vision with a paracentral hemianopic defect in the visual field of the homolateral eye. Paralysis of the oculomotor nerve and the not infrequent lack of cooperation on the part of the patient are often causes for overlooking small defects in the visual fields of patients with intracranial aneurysm.

CASE 1.[10]—*Aneurysm at junction of posterior communicating and internal carotid arteries revealed at autopsy in a patient originally thought to have retrobulbar neuritis; sudden unilateral loss of vision only symptom described at first*

9. Wagener, H. P., and Foster, R. F.: Ruptured Intracranial Aneurysms with Hemorrhages into the Retina and Vitreous, Proc. Staff Meet., Mayo Clin. **10**:225-229, 1935.

10. Previously reported in Walsh, F. B., and Ford, F. R.: Central Scotomas, Arch. Ophth. **24**:500-534 (Sept.) 1940.

examination, when slight pallor of nerve head was present; several weeks later, onset of severe pains in head and about right eye; spinal fluid bloody; ligation of internal carotid artery in neck in effort to control subarachnoid bleeding followed by contralateral hemiplegia and death.

J. J., a Negro man aged 29, was seen in the ophthalmologic dispensary on Jan. 4, 1940. He complained of almost complete blindness of the right eye, which had come on suddenly and developed in five days. There were no associated symptoms. He was an alcohol addict. Examination showed the right eye to be blind. The pupil was dilated and fixed to stimulation by direct light. The nerve head showed questionable pallor. A tentative diagnosis of retrobulbar neuritis was made. The blood pressure was 150 systolic and 80 diastolic, and there was a blowing murmur at the apex of the heart. The Wassermann reaction of the blood was positive. Roentgenograms of the skull were normal.

The patient disappeared from observation for several weeks, but on March 27 he was brought to the hospital in a semicomatose state. His friends related that he had had severe pains in the head for a month. On the morning of admission there was a severe exacerbation of the pain and he rapidly lost consciousness.

The temperature, the pulse rate and the respiratory rate were 99.8 F., 98 and 24, respectively. The neck was rigid, and the patient did not react to painful stimuli. Combativeness made examinations difficult. The pupils were widely dilated and were fixed to light. There were slight ptosis of the right upper lid and slight external deviation of that eye. The right optic nerve was chalky white and the left normal. A lumbar puncture produced bloody fluid on which a serologic test for syphilis gave a positive result.

The diagnosis of ruptured aneurysm seemed obvious. After occluding the right common carotid artery in the neck by pressure without appreciable change in the patient's condition, it was decided to ligate the right internal carotid artery in an effort to control the subarachnoid bleeding. Eighteen hours later flaccid left hemiplegia doveloped. The temperature mounted rapidly, and the patient died on the following day. Autopsy revealed a ruptured fusiform aneurysm of an anomalous posterior cerebral artery. This anomalous artery replaced the posterior communicating artery and had its origin from the middle cerebral artery. It was at the junction of these vessels that the aneurysm ruptured, and it had pressed directly on the right optic nerve. Histologic sections of the aneurysmal wall demonstrated the congenital defects already described.

This case represents an example of the commonest site in our series of aneurysmal formations, namely the internal carotid artery near or at the junction of the posterior communicating artery. In several similar cases the visual loss was insignificant. It is possible that in some of these cases we overlooked field defects. Jefferson cited several cases of aneurysm in this location which produced paracentral homolateral defects and temporal contralateral field defects. The absence of retinal subhyaloid hemorrhages in a case of such severe involvement is noteworthy.

CASE 2.—*Loss of vision which rapidly became complete in right eye of elderly woman; visual field of left eye showed nasal hemianopic defect; faint suprasellar calcification apparent in roentgenograms; complete absence of history of pain and no ocular palsies; large aneurysm of right internal carotid artery revealed*

by operation; death after spontaneous rupture of this aneurysm twenty-four hours after operation; additional aneurysm on left internal carotid artery revealed by autopsy.

This patient was seen by one of us (F. B. W.) through Dr. A. D. Ruedemann and Dr. W. J. Gardner, of the Cleveland Clinic. The preoperative diagnosis was suprasellar meningioma compressing the right optic nerve and the left optic tract. The case exemplified the bilateral occurrence of saccular aneurysms and the possible resultant visual field defects. The visual field defects in this case suggested bilateral lesions,

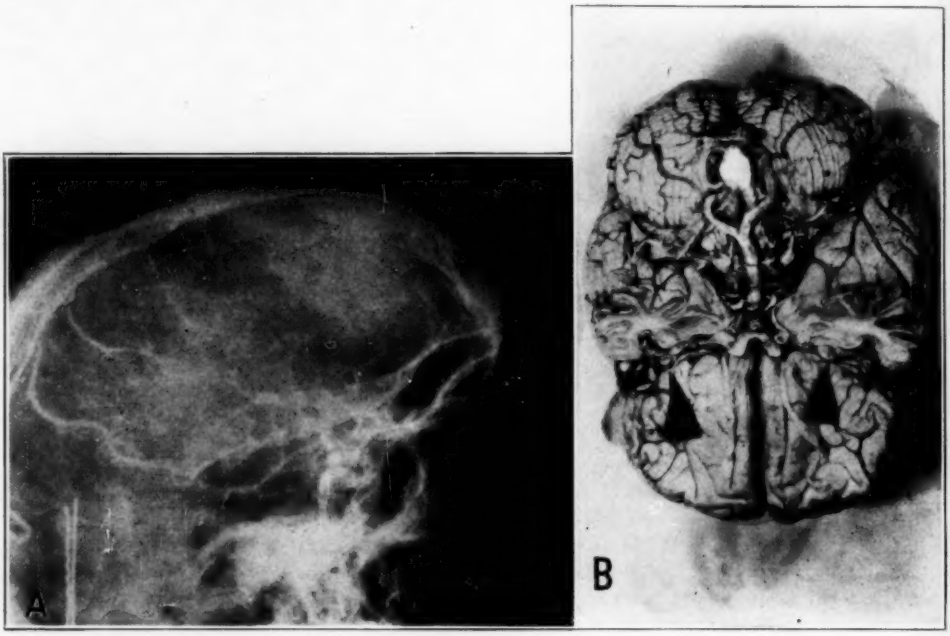

Fig. 2 (patient N. S.).—*A*, colloidal thorium dioxide injection of the brain showing one of the bilateral symmetric aneurysms which were erroneously thought to arise from the internal carotid arteries but which in reality were on the middle cerebral arteries. *B*, photograph of the base of the brain showing the bilateral symmetric aneurysms on the middle cerebral arteries and a third aneurysm at the distal end of the basilar artery (tips of the temporal lobes removed for exposure).

but the possibility of bilateral aneurysms was not considered before operation. Our experience leads us to believe that multiple aneurysms are common. In the case of N. S., summarized in the appended table, in which there were no localizing signs, study by means of injections of colloidal thorium dioxide in the carotid arteries demonstrated an aneurysm on each side (fig. 2 *A*). At autopsy four aneurysms were found, three of which can be seen in a photograph of the brain (fig. 2 *B*).

CASE 3.—*Unilateral oculomotor nerve paralysis with slight loss of vision and hemianopic paracentral visual field defect, all on right, due to supraclinoid aneurysm; patient a woman aged 40; influenza and otitis media with recovery in five days followed by pain in region of right eye; several weeks later, ptosis of right upper lid; then almost complete oculomotor nerve paralysis on the right; death following operation at which aneurysm was observed.*

T. G., a white woman aged 40, in February 1939 had an attack of influenza. During the attack otitis media on the right without a discharge developed. She was ill for five days, but on recovery she complained of a mild pain in the upper inner angle of the right orbit. She was told she had ethmoiditis. This pain persisted and became more severe, and late in April the upper right lid dropped. Treatment for sinus infection was continued.

Examination showed almost total oculomotor nerve paralysis on the right. The vision was 20/40 in the right eye and 20/20 in the left. The fundi were normal. The right visual field contained a hemianopic paracentral scotoma for small white objects. Otherwise the general physical, neurologic and roentgen examinations gave negative results. A diagnosis of saccular aneurysm of the supraclinoid type was made, and operation was advised.

At operation a bulge was seen on the outer side of the internal carotid artery extending to the region of the cavernous sinus. A clip was placed on the internal carotid artery below the origin of the anterior cerebral artery, and the internal carotid artery was then ligated in the neck. Complete left hemiplegia developed, and the patient died within a few days.

At autopsy an extensive infarction of the right cerebral hemisphere was discovered. An aneurysm was present about the origin of the posterior communicating artery.

Aneurysms Accounting for Bitemporal Field Defects.—The position of the anterior cerebral and anterior communicating arteries in relation to the optic nerves and the chiasm makes it obvious that aneurysms arising from them are likely to produce field defects. In some instances bitemporal defects, commencing usually in the lower fields, have been observed. In others total blindness of sudden onset has arisen as a result of chiasmal compression. However, small aneurysms may not produce any demonstrable field defects.

CASE 4.[10]—*Aneurysm of anterior communicating artery causing long-continued persistent headaches, defective visual acuity, photophobia, diplopia; operation on sinuses without relief of symptoms; vascular hypertension, mental confusion, continuous low grade fever and probable coarctation of aorta found on examination; roentgen evidence of involvement of posterior sinuses; ill defined temporal field defects; second operation on posterior sinuses and evacuation of sterile pus without relief; aneurysm revealed by craniotomy but ligation of carotid artery contraindicated; death from spontaneous rupture three months later.*

W. G., a white man aged 41, was admitted to the Johns Hopkins Hospital Jan. 11, 1939. The vision had been poor in both eyes for eight months; there had been pain on exposure to light for three months and there was discomfort in the frontal regions. He had been kicked in the head by a mule at the age of 10 years and had been hospitalized for vascular hypertension in 1920 and 1937.

In April 1938, after having had headaches for several weeks, he had a convulsion. He was admitted to a local hospital for study. Examinations included

two lumbar punctures. No diagnosis was made other than vascular hypertension. In October 1938 an operation was performed on the sinuses, but the headaches continued in spite of this.

Double vision had occurred two months previous to examination. There was a complaint of dyspnea on exertion, with an indefinite history of pains in the pre-

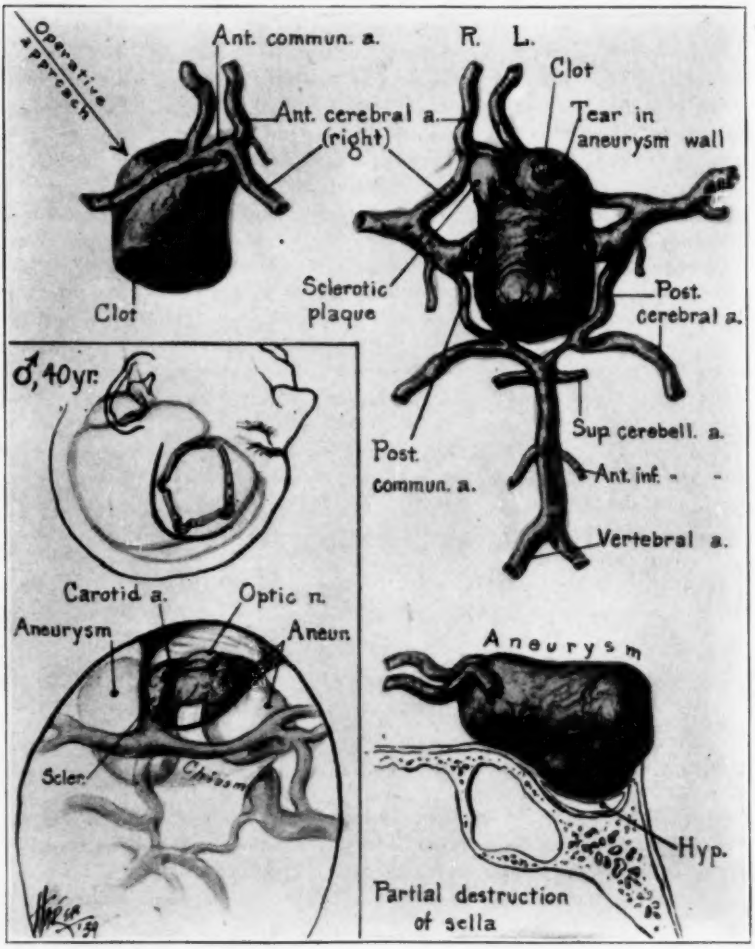

Fig. 3 (case 4).—Location of the aneurysm.

cordium and extending down the left arm. There were irregular periods of "roaring" in the right ear.

The patient was well developed. He was uncooperative and constantly complained that light was hurting his eyes. There was no audible bruit over the skull, nor was tenderness elicited over the bones, sinuses or mastoid processes. Examination of the nose, throat and teeth did not reveal anything abnormal. The lungs were clear, and the heart sounds were normal except for a short localized

harsh systolic murmur heard over the pulmonic area. No abnormalities of the abdomen were noted. Inability to obtain blood pressure readings in the legs suggested the possibility of coarctation of the aorta.

Examination of the eyes showed them normal externally except for redness of the conjunctiva and a slight irregular dilatation of the right pupil. The vision was 20/50 in the right eye and 10/200 in the left. The nerve heads were slightly pale; the retinal vessels were normal. Irregular temporal field defects were charted on several occasions. Roentgenograms of the skull showed dense clouding of the sphenoid sinuses and suggested destruction of the left clinoid process. A film of the chest revealed notching of the posterior aspect of the ribs characteristic of coarctation of the aorta. Serologic tests for syphilis (both of the blood and of the spinal fluid) were negative.

The patient continued to have an elevated temperature and was constantly drowsy. Leukocyte counts varied between 7,000 and 10,000. A recurrence of the sinusitis and some lesion about the chiasm were considered. On the basis of the coarctation and the temporal field defects it was suggested (by Dr. Frank R. Ford) that there was an aneurysm of the anterior cerebral artery, probably on the right side. Exploratory operation on the sphenoid sinuses revealed that the right was filled with creamy pus and that the left contained serosanguinous material; cultures were sterile. On February 8 Dr. Dandy explored the chiasm and found an aneurysm projecting between the chiasm and the optic nerves. Nothing further was done because a previous test of compression of the common carotid artery had produced dizziness within thirty seconds.

After the intracranial operation the patient's condition improved until April 8, when he suddenly had a generalized convulsion. A lumbar puncture revealed grossly bloody fluid. He died within a few hours. At autopsy it was shown that the aneurysm had ruptured. It was attached to the anterior communicating artery almost exactly in the midline, and it had compressed the chiasm and the hypothalamus. The pressure on the hypothalamus had probably caused the peculiar mental state and the constant elevation of the temperature.

Aneurysms involving the anterior cerebral and the anterior communicating arteries have been described largely from a pathologic standpoint by Courville and Olsen.[11] Russell [12] reported on the excision of an aneurysm arising from the anterior communicating artery. Dandy placed a clip on the neck and shriveled the sac of an aneurysm arising from the junction of the carotid and the posterior communicating artery. Case 4 exemplifies bitemporal field defects, but these could not be demonstrated to involve principally the lower quadrants.

Aneurysms Not Usually Attended by Loss of Vision (Intracavernous Aneurysms).—Saccular aneurysms arising within the cavernous sinus (subclinoid) usually do not produce visual field defects or loss of vision. They constantly produce pain in and about the eye and paralysis of the oculomotor nerve and often cause unilateral exophthalmos. Purely

11. Courville, C. B., and Olsen, C. W.: Miliary Aneurysm of the Anterior Communicating Artery: Clinical and Pathologic Report of Nineteen Cases, Eighteen with Fatal Hemorrhage, Bull. Los Angeles Neurol. Soc. **3**:1-21, 1938.

12. Russell, C. K.: Spontaneous Subarachnoid Haemorrhage Following Rupture of a Congenital Aneurysm of the Anterior Communicating Artery of the Circle of Willis, Tr. Am. Neurol. A. **65**:130-134, 1939.

intracavernous aneurysms are relatively uncommon in our experience, since the aneurysms in only 2 cases unquestionably belonged to this type. From the position of an aneurysm within the sinus it might be anticipated that the third, fourth, sixth and first divisions of the fifth nerves would all be about equally liable to involvement (so-called syndrome of the lateral wall of the cavernous sinus), but this does not seem to be the case. It is not unusual for an intracavernous aneurysm to extend anteriorly into the chiasmal region or posteriorly into the region of the posterior communicating artery, when the signs are those of aneurysm originating in those regions.

CASE 5.—*Aneurysm in cavernous sinus; severe pain in right eye for three days, with sudden increase followed by unconsciousness; diplopia and gradually increasing third nerve palsy; intracranial bruit; partial ligation of internal carotid artery in neck; persistence and progress of symptoms; reoperation and ligation of internal carotid artery intracranially; later, complete ligation in neck; improvement in ocular movements but paralysis of accommodation and persistence of bruit.*

D. R., a white woman aged 38, was first seen on April 9, 1938 complaining of drooping of the right upper lid. There was a questionable history of bilateral otitis media six years before, and for five years she had had occasional mild headaches.

Four months before examination she experienced a peculiar pain in the right eye, and after three days this pain became excruciating. She became unconscious but rapidly recovered, although nausea and vomiting persisted for some time. Slight drooping of the right upper lid was observed at this time. She gradually improved for a week; then the entire episode was repeated and the oculomotor palsy became pronounced. Her physicians heard a bruit over the skull, but the patient was at no time conscious of any intracranial murmurs. A partial ligation of the internal carotid artery in the neck was performed. A ventriculogram was reported as negative. The patient stated that at one time she had had considerable exophthalmos, but this had disappeared before she entered the Johns Hopkins Hospital.

General physical examination gave negative results. A systolic bruit was heard best over the left eye and faintly over the right eye. The right eye was slightly more prominent than the left, but, since it was deviated outward, accurate measurements were not possible. There was complete paralysis of the right oculomotor nerve, but function of the right fourth and sixth nerves was preserved. The vision was 20/40 in the right eye, and with a + 3.00 D. sph. the patient could read Jaeger test type 1 with that eye. The vision in the left eye was 20/15. The optic fundi were normal. Visual field defects could not be made out. Corneal sensitivity was normal.

Operation revealed an aneurysm within the cavernous sinus. The internal carotid artery was ligated intracranially, and nine days later it was occluded in the neck. The bruit remained unchanged after operation.

The patient was seen again in 1939, when there was considerable movement in the right upper eyelid. The internal rectus muscle had regained some of its power, but the internal ophthalmoplegia persisted unchanged. Visual acuity was 20/20 in the right eye and 20/15 in the left.

This case illustrates improvement in the function of the third nerve with, however, persistence of internal ophthalmoplegia. We have not observed the complete loss of corneal sensitivity so commonly found by

Jefferson and others in association with aneurysms in this situation. It is interesting that, while third nerve palsies are common and corneal hypesthesia is frequent, there is general agreement that the fourth and sixth nerves are rarely involved. The reason for this is not clear.

Aneurysmal Involvement of the Optic Tracts Resulting in Incongruous Hemianopia.—Jefferson remarked on the rarity of tract and radiation involvement by aneurysms. We have observed only 1 instance in which the field changes pointed to such a defect, and in this case the presence of an aneurysm, while clinically certain, was not proved. Operation was not performed, and the patient recovered spontaneously.

CASE 6.—*Aneurysm involving optic pathways and producing homonymous incongruous paracentral defects in visual fields.*

C. F., a white man aged 44, was seen in March 1937. He had suffered from migraine headaches for many years. In April 1936 he had a sudden headache not similar to those to which he was accustomed, and it was accompanied by vomiting and mental confusion. His pulse became slow and the temperature elevated. Lumbar puncture revealed blood in the spinal fluid. It was then shown that the visual fields contained incongruous homonymous paracentral defects in the upper right portion which could be due only to a lesion involving the optic tract or radiation.

Posterior Aneurysms Accounting for Ocular Signs and Simulating Cerebellar Neoplasms.—In our available material there are only three examples of saccular aneurysms at this level.

CASE 7.—*Aneurysm of left vertebral artery accounting for bilateral sixth nerve palsy, ptosis of left upper lid and nystagmus in attempted right lateral gaze; no changes in optic fundi, visual acuity or visual fields; other neurologic signs pointing to tumor of right hemisphere of cerebellum.*

M. J. R., a white woman aged 18, was first seen in March 1937, when she complained of choking spells, some difficulty in talking and stiffness of the neck. All these symptoms had been present for several weeks. Early in April she continued to complain of pain in the neck, and diplopia had developed. Fluids were regurgitated through the nose. She complained of dizzy spells and could not lie with her head completely flat, and her gait had become unsteady.

Examination showed bilateral sixth nerve palsy, nystagmus with the eyes in attempted right lateral deviation, vertical nystagmus and slight ptosis of the right upper lid. Visual acuity was 20/20 and 20/30 in the right and in the left eye, respectively. The optic fundi and the visual fields were normal. Roentgenograms of the skull and of the sella turcica were not remarkable. A ventriculogram revealed a deformity in the floor of the third ventricle and symmetric dilatation of the lateral ventricles, but the aqueduct and the fourth ventricle were not visualized

Operation was performed, but the cerebellum did not contain a tumor. When the vermis was split an aneurysm was discovered lying below. Severe bleeding was encountered, and the patient failed to recover.

At autopsy a ruptured aneurysm was seen attached to the left vertebral artery in such a way that it pushed the medulla and the cord to the right.

CASE 8.—*Aneurysm of basilar artery which produced choked disks and signs suggestive of cerebellar neoplasm; complete absence of extraocular palsies and nystagmus.*

B. S., a white man aged 27, was admitted Sept. 27, 1915 complaining of difficulty in speaking and walking.

In October 1914 he had begun having occipital headaches and in September 1915 had commenced having difficulty in talking, his speech becoming thick and blurred. He then noticed that while walking he would stagger, and soon after difficulty in swallowing developed. Examinations showed motor aphasia, bilateral high grade papilledema and absence of the gag reflex. Fluids were expelled through the nose. There was slight ataxia of the legs, and the Romberg sign was present. The reflexes were exaggerated, particularly on the left.

A diagnosis of cerebellar tumor was made. The patient died after an exploratory operation at which a tumor was not discovered.

Autopsy revealed an aneurysm of the basilar artery producing a pressure displacement of the pons and closure of the aqueduct of Sylvius.

PART II. OCULAR SIGNS HITHERTO UNDESCRIBED AS ASSOCIATED WITH SACCULAR ANEURYSMS

Misdirection of fibers in regeneration of the third nerve results in an anomalous movement of the lid. This has been described by Bielschowsky,[13] Bender [14] and Ford and Woodhall.[15] Its frequent occurrence as a result of aneurysm has not been mentioned.

Mass movement and "facial contracture" have long been recognized as developing after regeneration of the facial nerve. The distortion of the face, present when the patient is under emotional stress, indicates that numerous stimuli play on the facial muscles under such circumstances (Ford and Woodhall). The mechanisms in the case of regenerated third nerves are somewhat different. When an effort is made to move the eye in any direction, impulses flow at the same time into all the muscles innervated by the third nerve. Movement up or down does not occur, since the superior and the inferior rectus muscle contract together and the pull is balanced. However, since at the same time the internal rectus and the levator palpebrae muscle receive stimuli the eye turns in and the lid is elevated. The phenomenon of course is not always fully developed, since regeneration may not be complete and the amount

13. Bielschowsky, A.: Lectures on Motor Anomalies of the Eyes: Paralysis of Individual Eye Muscles, Arch. Ophth. **13**:33-59 (Jan.) 1935.

14. Bender, M. B.: Contractions in Denervated Muscles Induced by Fright as Evidence of Secretion of the Parasympathetic Hormone, J. Mt. Sinai Hosp. **5**: 411-418, 1938. Bender, M. B., and Weinstein, E. A.: Actions of Adrenaline and Acetylcholine on the Denervated Iris of the Cat and Monkey, Am. J. Physiol. **130**:268-275, 1940. Bender, M. D.: The Nerve Supply to the Orbicularis Muscle and the Physiology of the Movements of the Upper Eyelid, with Particular Reference to the Pseudo-Graefe Phenomenon, Arch. Ophth. **15**:21-30 (Jan.) 1936.

15. Ford, F. R., and Woodhall, B.: Phenomena Due to Misdirection of Regenerating Fibers of Cranial, Spinal and Autonomic Nerves: Clinical Observations, Arch. Surg. **36**:480-496 (March) 1938.

of misdirection may vary. In actual practice the anomalous elevation of the lid often is minimal and the sign is likely to be overlooked. We have observed associated movement of the pupil in a case about to be described.

CASE 9.—*Saccular aneurysm of internal carotid artery, in a man aged 58, treated by partial ligation of artery in neck and a month later by intracranial ligation; degeneration of third nerve producing abnormal movements of lid*

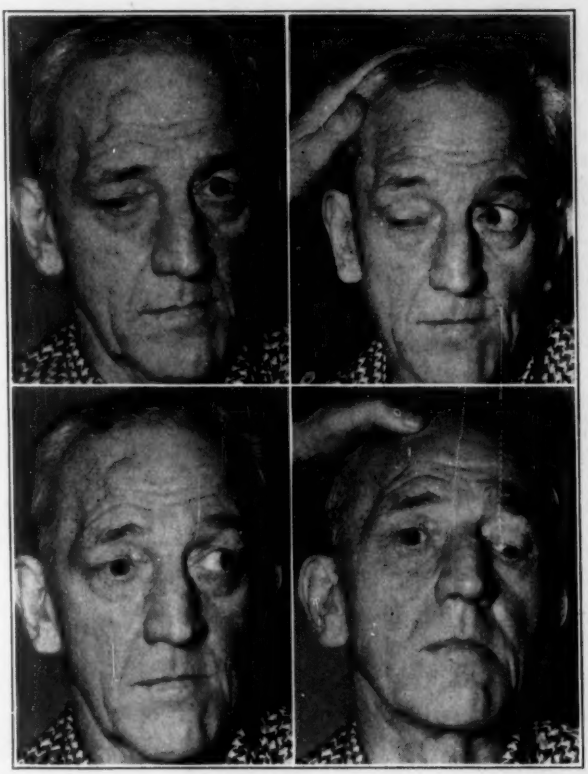

Fig. 4 (case 9).—Regeneration with misdirection of fibers. When adduction or downward movement was attempted the lid became elevated.

associated with ocular movements; partial recovery from internal ophthalmoplegia; abnormal pupillary movements.

H. K., a white man aged 58, was first seen on April 12, 1940, when he was brought to the hospital in a semiconscious state. There was a history of his having had a short spell of unconsciousness some ten years previously. He had been an alcoholic addict for several years.

Two days before admission the patient complained of severe pain in the back of the neck and of frontal headache. On the following day he became irrational and combative and his neck became very stiff. On admission, general examination gave essentially negative results but a lumbar puncture yielded bloody fluid. The

blood pressure was 138 systolic and 70 diastolic. Neurologic examination showed stiffness of the neck, moderately hyperactive reflexes and bilateral Kernig signs. Seven days later weakness of the left arm and leg and a Babinski sign on the left were demonstrated. The headaches continued, and the patient remained irrational. Several days later a grasp reflex developed in the left hand and the left leg and arm became spastic. On May 14 partial oculomotor nerve paralysis developed on the right. The diagnosis of aneurysm of the circle of Willis seemed justified. Ophthalmoscopic examination showed nothing significant save retinal arteriosclerosis.

Partial ligation of the right internal carotid artery in the neck was performed on May 16. Thereafter improvement in the general condition was rapid, but there was now complete oculomotor nerve paralysis on the right. The spastic left hemiplegia persisted. On June 13 Dr. Dandy did a craniotomy on the right and found the carotid artery on that side adherent to the base of the skull. It was determined that an aneurysm was present, but its position was not made out with complete certainty. A clip was placed on the carotid artery below the anterior cerebral and the posterior communicating artery in front of the aneurysmal dilatation. Recovery was uneventful.

The initial improvement was lessening of the ptosis. Before it was possible to adduct the eye beyond the midline, efforts to do so elevated the upper lid slightly. Within two weeks after this movement had been noted the pupil was observed to contract when efforts were made to adduct the eye. At this time efforts to look inward and down resulted in prompt elevation of the upper lid. The range of adducting and downward rotation returned to about half normal within six months.

At the time of writing (March 18, 1941) the vision was 20/25 in the right eye and 20/30 in the left. The ptosis had disappeared. It was observed that on adduction of the eye the pupil contracted, but contraction was most pronounced when the patient fixed on a near object. Stimulation by light directly and consensually failed to produce contraction of the pupil.

This and the following case illustrate misdirection of regenerated nerve fibers. In addition they illustrate pronounced improvement in internal ophthalmoplegia. We have observed other cases in which the internal ophthalmoplegia did not improve even though the external ophthalmoplegia did so to a marked degree. The pupillary reactions in this case are of particular interest. The associated movement of the pupil on adduction of the eye is of particular importance, since in the eye there has developed a type of unilateral Argyll Robertson pupil. This case and 2 others, summarized in the table (those of B. F. and M. F.), occurring in such a small series are most significant.

Another case exemplifies misdirection of fibers in the third nerve. Our failure to recognize this as a regenerative syndrome resulted in an error in diagnosis and disregard of true localizing signs.

CASE 10.—*Postmortem diagnosis of arteriovenous communication in left occipital region with hemorrhage into ventricles and base, unruptured saccular aneurysm of right internal carotid artery; death from intracranial hemorrhage.*

E. H. M., a Negro aged 50, entered the hospital on May 6, 1939 in a confused state. He complained of headaches and exhibited partial ptosis of the right upper eyelid. A reliable history was available from a relative.

The entire left side had always been somewhat weaker than the right. For several years before admission he had complained of intermittent headaches in the right frontal region. After the first severe headache there were ptosis of the right upper lid and diplopia. The headaches continued at intervals of from seven to ten days, with each attack lasting about twenty-four hours. The ptosis gradually improved, but the diplopia persisted. About three months before admission he had noticed a defect in the right side of the visual field of each eye. About two weeks before entry into the hospital he again complained of severe headaches and noticed recurrence of ptosis of the right upper lid. Three days before he was seen the headaches became very severe and he lost consciousness for several hours. After this episode he was drowsy and complained of stiff neck. A lumbar puncture was said to have yielded bloody fluid.

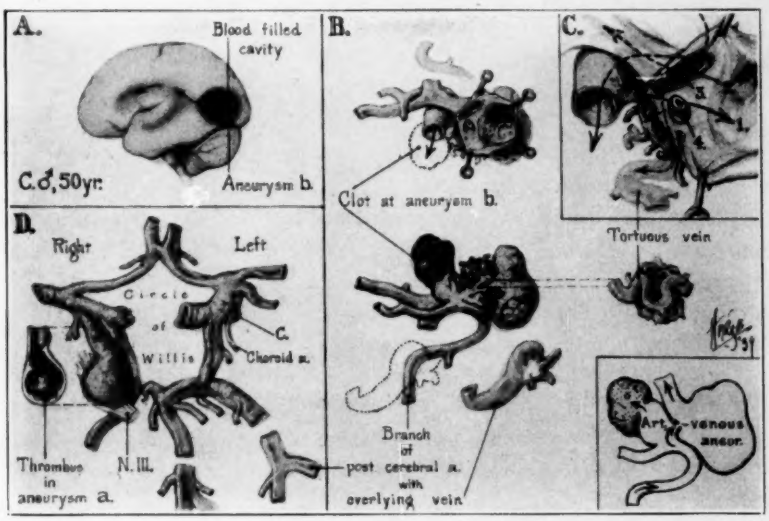

Fig. 5 (case 10).—Drawing of the involvement observed at autopsy.

Examination of the right eye showed intermittent ptosis. There was almost complete inability to elevate or lower the eye, but it could be adducted, and with this movement there was slight elevation of the upper lid. The vision was 20/50 in the right eye and 20/40 in the left. Retinal hemorrhages were present in each eye, and the disk margins were blurred. The pupils were equal and reacted to light. The visual fields were normal for form but on the right showed a homonymous hemianopic defect for colors. The reflexes were sluggish on the right and normal on the left. There was slight ataxia of the left arm. Roentgenograms showed thinning and partial destruction of the posterior clinoid processes, more pronounced on the left.

A tentative diagnosis of saccular aneurysm on the right side of the circle of Willis was made. Attention was drawn to the homonymous hemianopia and the sluggish reflexes on the right, both of which were difficult to explain on the basis of a lesion on the right side.

At operation the right frontal lobe was resected and free blood was observed lying under the left frontal lobe. An aneurysm was found on the right internal

carotid artery. It was filled with a thrombus and was not the source of the bleeding. Further search failed to reveal the origin of the hemorrhage. The patient failed to rally and died after several days.

Autopsy showed an arteriovenous communication in the left occipital lobe with hemorrhage into both the ventricular system and the subarachnoid space. The saccular aneurysm on the right internal carotid artery was unruptured. A small unruptured saccular aneurysm was present on the left internal carotid artery.

Denervation Phenomena Dependent on an Intracranial Aneurysm.—A pseudomotor and a pupillary phenomenon were observed in the same person. These are important in regard to recent work in physiology. The patient, a man of 23, had exhibited what appeared to be complete oculomotor nerve paralysis on the left for fifteen years. At irregular intervals the left lid surged open and remained elevated for a few seconds or for as long as several minutes. There was no associated change in the size of the pupil or in the position of the eye. The elevation might occur spontaneously or might be produced by bathing of the face in cold water. The patient stated that elevation of the lid invariably appeared when he lost his temper or became interested in an attractive member of the opposite sex.

A chemical sensitivity was shown to produce a contraction of the apparently paralyzed pupil when solution of mecholyl chloride was dropped into the conjunctival sac of each eye. The pupil which was widely dilated promptly contracted to about 2.5 mm., whereas the pupil in the normal eye did not change its size.

These phenomena exemplify Cannon's [16] law of denervation. Cannon stated that postganglionic and, to a lesser degree, preganglionic section of any nerve result in increased sensitivity of the innervated structure to the chemical mediator, whether that mediator is sympathin or acetylcholine. The sensitivity persists providing that regeneration does not occur and that the innervated structure does not become atrophic.

The elevation of the lid in our patient was identical with that observed by Bender in experimental animals. Bender produced denervation by severing the third nerve intracranially in monkeys. Physiologic stimuli, fright and anger, caused the upper lid to become elevated. This reaction was also obtained by the injection of acetylcholine hydrochloride protected with physostigmine salicylate. The reaction persisted until regeneration was complete. Unfortunately we did not protect the acetylcholine hydrochloride when giving injections to our patient. Intravenous injection of epinephrine hydrochloride failed to produce the phenomenon. Since the circumstances preceding the elevation of the lid were the same as those observed by Bender, an identical mechanism was probably responsible.

16. Cannon, W. D.: A Law of Denervation, Am. J. M. Sc. **198**:737-750, 1939.

CASE 11.—*Man of 23 suffering probably from leak from aneurysm which developed at age of 2 years; there gradually developed paralysis of left oculomotor nerve which was complete at 8 years; spontaneous elevation of left upper eyelid; pupillary contraction of the left eye promptly resulted from instillation of mecholyl chloride; unexplained exophthalmos; amblyopia exanopsia?*

J. F., a white man, 23, was examined in April 1939. When he was 2 years old he had a sudden severe pain in the head, and on the following day there was slight drooping of the left upper lid. This ptosis gradually became more pronounced and was complete at the age of 8 years. It remained constant except for brief periods when the upper eyelid spontaneously lifted. Washing his face with cold water sometimes induced the elevation, but anger or fright always caused the phenomenon to appear. It was not associated with either active or passive movements of the jaw. For six or eight years he had complained of a dull throbbing pain in the left temporal region. Occasionally this was interspersed with stabs of pain radiating to behind the left ear. For five years he had had a few grand mal seizures, but during the year before examination only two seizures had occurred.

There was complete cculomotor nerve paralysis on the left. The left eye was proptosed; exophthalmometric readings were: right eye, 17; left eye, 21. The vision was 20/15 in the right eye and 10/400 in the left. Ophthalmoscopic examination revealed normal fundi. The visual field of the left eye showed a large central scotoma. The causation of the defect was obscure. The course was thought to be too long for a diagnosis of aneurysm, but the same objection seemed to apply to a diagnosis of neoplasm. Roentgenograms of the optic foramens were normal, but an area of calcification was present to the left of the sella turcica. Other examinations gave negative results.

A craniotomy on the left was performed by Dr. W. E. Dandy, and an aneurysm bulged from the cavernous sinus. The internal carotid artery was ligated intracranially and in the neck. Recovery was uninterrupted.

A year later the patient stated that he had not had further convulsions. The vision, the visual fields and the lid phenomenon were unchanged.

PART III. EXPERIMENTAL STUDIES

Patients who are treated by the "trap" operation, which was devised by Dandy for aneurysms arising from the carotid artery, rarely sustain diminution of vision in the homolateral eye. One ligation is performed in the neck, and the other is done intracranially distal to the origin of the ophthalmic artery. Thus the ophthalmic artery is isolated between the ligatures. Since patients subjected to this operation do not become blind, it is apparent that an adequate collateral circulation exists between the ophthalmic artery and the branches of the external carotid artery.

Elschnig was the first to demonstrate the rich anastomosis between the terminal arteries arising from the external carotid and the ophthalmic artery. He conducted experiments on human cadavers and showed that after the occlusion of the internal carotid artery intracranially, water and water-soluble dyes injected into the common carotid artery would by retrograde flow appear in the distal segment of the ophthalmic artery.

Our experiments were carried out on adult human beings, all of whom had died at least five days before. In all instances the "trap" operation was performed. The internal carotid artery was ligated at the bifurcation of the common carotid artery and intracranially distal to the ophthalmic artery. A 20 cc. Luer syringe was used to inject the fluid.

EXPERIMENT 1.—After the double ligation of the internal carotid artery a highly colored solution of methylene blue was injected into the common carotid artery on the same side. The fluid flowed in with ease, and the face and the sclera on that side turned blue. The skin on the opposite side also became discolored, especially about the nose and cheek. After 40 cc. of the fluid had been injected it was observed flowing out of the distal cut segment of the ophthalmic artery at a rapid rate. It was evident that many vessels arising from the external carotid artery anastomose with branches of the ophthalmic artery, producing a rich collateral circulation. Since no dye was observed coming out of the proximal portion of the cut artery it must be assumed that there are no vessels of any considerable size emptying into the internal carotid artery. At the conclusion of the experiment the roof of the orbit was removed and the eye opened. The dye was easily visible in the conjunctival and scleral vessels.

This experiment confirms the work of Elschnig and at the same time provides an adequate explanation for the preserved vision after operations of the "trap" type. The next step was to provide a visual demonstration of the accessory blood supply.

EXPERIMENT 2.—The internal carotid artery was treated as in experiment 1. Injection was made of 60 cc. of colloidal thorium dioxide, and we again observed material escaping from the distal orifice of the severed ophthalmic artery. X-ray films recorded the rich circulation of the orbit on the same side. The trapped segment of the internal carotid artery did not visualize, and this again proves that no significant collateral vessels empty into this portion of the vessel.

In order to demonstrate some of the accessory vessels both visually and roentgenographically the next cadaver was injected with Weber's artist's water color vermilion according to the method described by Batson.[17] In this case the ophthalmic artery was left attached to the internal carotid artery.

EXPERIMENT 3.—The internal carotid artery was ligated as usual. The ophthalmic artery was isolated but left intact. The roof of the orbit was then opened and a considerable portion of orbital fat removed. The levator palpebrae and the superior rectus muscle were cut but left attached. To serve as a marker a silver clip was placed on the medial aspect of the optic nerve as it entered the bulb. A thin suspension of the vermilion paint was then injected into the common carotid artery. The face and sclera on the same side took on an orange hue. As with methylene blue, the cheeks and nose on the opposite side also became colored. Almost at once many minute vessels in the orbit exuded the red pigment. We concluded that many small arteries are derived from branches of the external carotid artery and that probably many of these orbital vessels unite with branches of the ophthalmic artery. After about 100 cc. of the solution had been

17. Batson, O. V.: Function of the Vertebral Veins and Their Role in the Spread of Metastases, Ann. Surg. **112**:138-149, 1940.

injected, roentgenograms were made. The interesting feature of these is visualization of the isolated portion of the internal carotid artery, as shown in figure 6. This illustration must portray the situation present after ligation of the internal carotid artery at operation and explains why the ophthalmic artery remains patent.

The next experiment was undertaken to demonstrate the patent ophthalmic artery. As a very radiopaque solution is needed to visualize such a small vessel a saturated watery solution of lead acetate was used.

EXPERIMENT 4.—The same procedures were carried out as in the previous experiments. In this instance, however, the orbit was opened carefully and disturbed as little as possible. A silver clip was placed on the medial aspect of the optic nerve where it enters the bulb. About 100 cc. of a saturated solution

Fig. 6 (experiment 3).—Isolated portion of the internal carotid artery filled with radiopaque material by retrograde flow through the homolateral ophthalmic artery.

of lead acetate was injected into the common carotid artery, and when the milky fluid was seen dripping from the cut end of the ophthalmic artery another silver clip was placed over the distal orifice. This second clip was placed almost at the junction of the internal carotid and the ophthalmic artery. Figure 7 *A* demonstrates the entire length of the ophthalmic artery, lying between the two clips.

After the roentgenograms were procured the clip on the artery was removed and about 200 cc. of tap water was injected into the common carotid artery to flush out the lead acetate solution. Then about 100 cc. of diluted solution of india ink was introduced. The face, conjunctiva and scleral vessels immediately changed in color to dark black. The eye was then removed along with the optic nerve. Microscopic sections showed particles of india ink in the central retinal artery (fig. 7 *B*).

Thus we have visual, pictorial and microscopic demonstrations of the filling of the ocular arteries by way of the external carotid circulation.

A final experiment was carried out to determine whether the ophthalmic artery in the contralateral orbit would fill by the way of the branches of the external carotid artery.

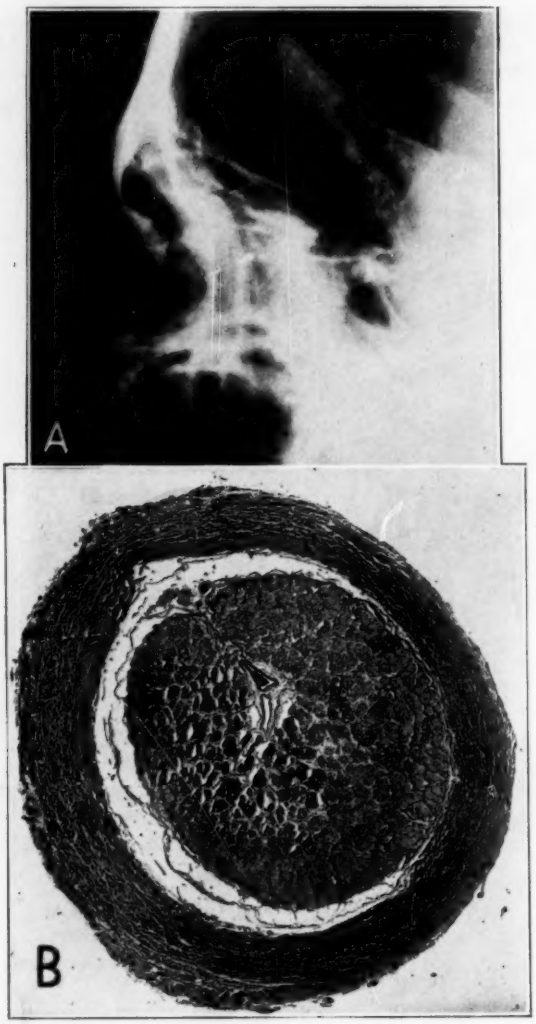

Fig. 7 (experiment 4).—*A*, homolateral ophthalmic artery filled by retrograde flow from the external carotid artery. *B*, demonstration with an india ink preparation of the filling of the central retinal artery.

EXPERIMENT 5.—In a cadaver both internal carotid arteries were ligated at the bifurcation of the common carotid artery and intracranially about 5 mm. distal to the ophthalmic artery. Both ophthalmic arteries were left intact. About 200 cc. of a thin suspension of barium sulfate was injected into the left common carotid

artery. The visualization of this vessel showed that the circulation across the midline was sufficient to fill the ophthalmic artery and the trapped segments of the two internal carotid arteries. This leads to the hypothesis that vision might well remain unaffected if both internal carotid arteries were ligated intracranially. However, such a procedure in all probability would produce severe cortical damage (fig. 8).

The experiments described show conclusively that a large collateral circulation exists between the external carotid artery and the ophthalmic artery of the same side and that there is sufficient cross circulation so that the ophthalmic artery of the contralateral side may be filled from

Fig. 8 (experiment 5).—The filling of the isolated segments of the two internal carotid arteries by injection of one external carotid artery. Both ophthalmic arteries were left intact. The segment on the right was difficult to photograph.

the external carotid artery. Visual roentgenographic and microscopic evidence has been produced to support these statements.

Clinical Cases.—We have mentioned that ligation of the internal carotid artery both above and below the ophthalmic artery has caused no impairment of vision. In 3 instances vision was impaired in the same eye, but in each case additional procedures were necessary owing to complicating factors. All the ligations observed by us have been carried out with the patient under general anesthesia. Whether transient diminution or loss of vision occurs we do not know. Mention was made by Birley and Trotter of transient blindness in the homolateral eye

resulting in some cases in which a ligature was applied either to the internal or to the common carotid artery in the neck. Consequently it is altogether likely that such transient blindness occurs in some instances when the ligation is performed intracranially. We have records of only 1 patient in whom the "trap" operation resulted in homolateral loss of vision.

CASE 12.—*Intracavernous aneurysm treated by ligation of internal carotid artery in neck and intracranially; only case in which muscle was introduced into lumen of isolated artery; also only instance in which homolateral blindness followed "trap" operation.*

L. B., a white woman aged 28, seen in September 1936, complained of severe headaches on the left side. Except for having had a recurrent hemangioma of

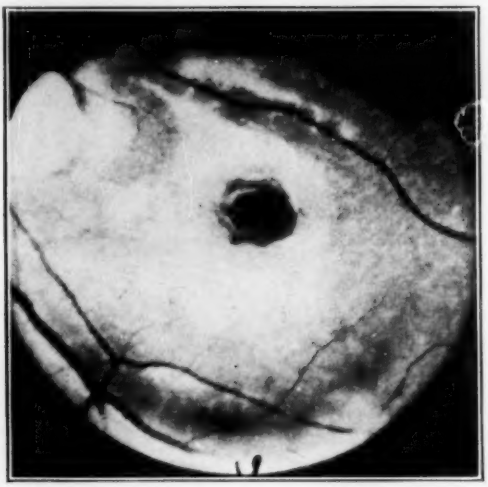

Fig. 9 (case 12).—Photograph of the fundus showing the results of closure of the central retinal artery.

the right thenar eminence, she had been well until the onset of the illness which caused her to come to the hospital.

During the summer of 1936 she had complained of generalized headaches. On August 14 she suffered a severe pain in the head and became semiconscious. The pain persisted for two days; then it partially subsided but recurred. She was admitted to a local hospital, where several lumbar punctures were done and the fluid was always found to be bloody. The punctures afforded relief, and she was discharged after twelve days. Ten days later pain in the head returned. On this occasion it centered in the left supraorbital region. The patient again entered the hospital, and lumbar puncture was performed, but on this occasion the fluid was clear. When she arrived in the Johns Hopkins Hospital she was conscious but not cooperative and complained of pain in the head.

Examination showed complete oculomotor nerve paralysis on the left, questionable seventh nerve paresis of the peripheral type and hyperactive knee jerks. Roentgenograms of the skull, sella turcica and sinuses were normal.

The diagnosis of aneurysm seemed clear. At operation a small bulging red mass, covered by dura, lay on the internal carotid artery, bulging in from the dura covering the cavernous sinus. The third nerve was pushed posteriorly by the aneurysm. A clip was placed on the internal carotid artery, and it was then exposed in the neck. With pressure on it, an opening was made cephalad to the place where it was being compressed. This resulted in free bleeding (due to collateral circulation through the ophthalmic artery of that side, since the internal carotid artery was tied distal to the orifice of the ophthalmic artery). In order to obtain thrombosis in the aneurysm a piece of muscle was placed in the lumen of the internal carotid artery, which was then securely ligated.

After operation the patient was almost completely blind in the left eye. Convalescence was uneventful. The picture in the left eye was that of embolus of the central retinal artery.

Two years later there was considerable recovery of the third nerve on the left, movement of the upper lid was almost normal and internal rotation of the eye was full. Visual acuity was limited to perception of light.

In this case muscle was introduced into the lumen of the artery with the object of producing thrombosis. Whether thrombosis extended up to and involved the ophthalmic artery or whether a small piece of muscle or an embolus lodged in the artery is a matter of conjecture.

This single example of visual loss as a sequela of the "trap" operation brings to mind patients who have sustained spontaneous closure of the internal carotid artery. This syndrome has recently been reviewed by King and Langworthy.[18] Acute spontaneous closure of the internal carotid artery is not common, and only a few case histories of persons in whom such closure has passed into the chronic state have been published. Thrombi that form in the internal carotid artery usually obliterate the lumen in the vessel quickly. When the artery is plugged by an embolus, a large thrombus quickly forms behind it and the clot may extend down through the common carotid artery. After sudden spontaneous closure of the internal carotid artery, the patient, according to our experience, always becomes blind in the homolateral eye. It would appear likely that the process accounting for thrombosis in the carotid artery also occludes the ophthalmic artery. Ophthalmoscopic examination reveals primary atrophy of the optic nerve and pronounced diminution in the size of the retinal arteries.

Damage in varying amounts occurs in the cerebral cortex, but this probably depends on the size of the communicating vessels of the circle of Willis and on how far the thrombus extends up the middle cerebral artery. The lesions produced may be so small as to produce only slight spasticity in the contralateral arm, loss of some fine movements in the hand and a Babinski reflex. However, marked hemiplegia, hemianopia in the field of the contralateral eye, aphasia and difficulty in swallowing occur if there is extensive softening.

18. King, A., and Langworthy, O. R.: Neurologic Symptoms Following Extensive Occlusion of the Common or Internal Carotid Artery, Arch. Neurol. & Psychiat. **46**:835-842 (Nov.) 1941.

Homolateral blindness and primary atrophy of the optic nerve are always present, according to our experience, in cases of thrombosis of the internal carotid artery, while the other signs may vary. There is consequently a fundamental difference between surgical isolation of the internal carotid artery and spontaneous occlusion due to thrombus.

Recently a patient appeared at the Baltimore City Hospitals presenting a picture not unlike that of spontaneous occlusion of the internal carotid artery. A careful study and evaluation of the cerebrospinal fluid changes, the history, the clinical findings and an arteriogram led to the diagnosis of aneurysm. The case history summarized hereafter is unique.

CASE 13.—*Aneurysm (?) accounting for signs of thrombosis of middle cerebral artery; picture, embolus of central retinal artery; sympathetic ptosis; small pupil which failed to dilate with cocaine.*

C. P., a white man aged 38, was admitted to the Baltimore City Hospitals on Oct. 9, 1940 with a complaint of weakness of the legs. The family and the personal history revealed nothing important except that the patient had been an alcoholic addict. The day before admission he partook liberally of alcohol and finally went to sleep in a lumber yard. The next morning he awoke, felt nauseated and vomited. Later in the morning he was taken in charge by the police. While being interviewed he suddenly fell, and he was immediately brought to the hospital.

Examination.—The temperature was 98, the pulse rate 66, the respiratory rate 26 and the blood pressure 150 systolic and 100 diastolic. The patient was well nourished and well developed and appeared his stated age. He was acutely ill, restless and trembling but oriented for time, place and person. He complained constantly of pain over the right side of the head. General physical examination gave negative results. Neurologic examination showed extensive changes. The eyes were kept closed, and he complained of constant pain in both but particularly in the right. Light increased the discomfort. The pupils were round, regular and equal. The left pupil contracted promptly to light, but the right reacted sluggishly. The extraocular movements were of full range, and there was no nystagmus. A satisfactory ophthalmoscopic examination could not be made because of lack of cooperation. There was facial paralysis of central type on the left, and the tongue deviated to the left. The left arm and leg were flaccid, and the patient was unable to move them voluntarily. The reflexes were about equal on the two sides, but there was a plantar response on the left. Laboratory examination showed no abnormalities of the urine, stool, red blood count or hemoglobin. The Wassermann reaction was negative. There were 17,000 white blood cells per cubic millimeter, with a differential count showing 80 per cent polymorphonuclear leukocytes. A lumbar puncture was done, and the pressure was 190 mm. of water with a normal response to jugular compression. The fluid was clear, but a count showed 600 red cells per cubic millimeter. The Pandy reaction was negative. Later a culture was reported as sterile and a Wassermann reaction was negative.

Course in the Hospital.—On the day after admission the patient became more cooperative, and a more detailed neurologic examination could be carried out. He was still restless and complained of pain in the right eye. The headache had disappeared, and the neck was not stiff. There was slight ptosis, enophthalmos and smallness of the pupil on the right. The corneal sensitivity was lowered in the

right eye. The vision was good in each eye, and the visual fields appeared normal on gross tests. Both pupils reacted promptly to light and in accommodation convergence. Ophthalmoscopic examination gave negative results. The left hemiplegia, facial and shoulder weakness and deviation of the tongue were now more pronounced. Tendon reflexes were hyperactive on the left, and there were Babinski and Oppenheim reflexes on that side. Roentgen examination of the skull failed to show any abnormality. The patient remained drowsy for several days, during which he slept most of the time. The Horner syndrome persisted, and a daily examination of the eyegrounds revealed no further changes. The right eye became tender to touch, but there was no evidence of infection. An encephalogram was attempted one week after admission, but the ventricles were not visualized. The spinal fluid had become xanthochromic and contained 80 mg. of protein per hundred cubic centimeters. On the tenth day after admission the ophthalmoscopic picture in the right eye was that of embolus of the central retinal artery. The disk was pale and hazy, and a cherry red spot was present at the macula. The arteries were reduced to minute threads. The ptosis on this side had become more pronounced. The vision was reduced to perception of light. It was now evident that the patient either had an aneurysm of the internal carotid artery which had been the source of an embolus or had sustained a thrombosis of the internal carotid artery.

Two days later, with the patient under local anesthesia, the right common carotid artery was exposed and 13 cc. of colloidal thorium dioxide was injected into the artery. Unfortunately the patient was not cooperative, and a satisfactory film was not obtained. The injection was repeated one week later, and a reasonably satisfactory arteriogram was obtained. The internal carotid artery was patent. A ringlike structure was visualized just lateral and anterior to the sella turcica. Accordingly a diagnosis of intracerebral aneurysm, probably of the right internal carotid artery, was made.

In another week the ptosis had regressed. The right pupil was slightly contracted and irregular. It did not react to direct light but reacted promptly to consensual light stimulation and in convergence. The right eye was blind. The fundus had now changed, and the macular region was clear except for a small patch of white material which had persisted. The nerve head was pale, and the arteries were threadlike. There was no complaint of pain in the eye at this time. The extraocular movements continued to be normal.

A craniotomy on the right was performed on November 30. The internal carotid artery was patent, and no aneurysm was found. No abnormality of the intracranial portion of the carotid artery or of the proximal portion of the anterior cerebral and the posterior communicating artery could be demonstrated. Both ophthalmic arteries seemed normal.

This case is included in spite of the fact that an aneurysm was not demonstrated at operation. Whether the true diagnosis was thrombosis of the middle cerebral and the ophthalmic artery or an intracavernous aneurysm producing multiple emboli is at present undecided. However, since the clinical findings were so typical of aneurysm we feel that operation was justified.

Information regarding all the aneurysms we have seen, including those in the cases already described, is presented in the table. The clinical course for the most part has not been considered.

Patient	Sex; Race	Age, Yr.	Ocular Symptoms: Pain in Eyes	Ptosis	Status of Pupils	Other Ocular Palsies	Retinal Hemorrhage	Subhyaloid Hemorrhage	Choked Disk	Field Defects; Visual Acuity	Other Neurologic Signs	Operative or Postmortem Observations
Baltimore City Hospitals												
E. M.	♀ Negro	50	.....	No	Equal; reacted normally	No	In both eyes	No	No	Not determined	Babinski sign, right; Wassermann reaction negative	Aneurysm, junction of anterior communicating and left anterior cerebral artery; subarachnoid hemorrhage
F. D.	♂	72	.....	No	Left > right; no reaction to light; reaction in convergence	No	No	No	No	Not determined	Left hemithalamic syndrome; bilateral Babinski signs; blood and cerebrospinal fluid, Wassermann reaction positive	Bilateral aneurysms, junctions of anterior communicating and anterior cerebral arteries
M. T.	♀	80	.....	.....	Equal; reacted	.....	No	No	No	Not determined	Raynaud's disease, hands and feet; unconscious on admission; blood in spinal fluid	Aneurysm, junction of posterior communicating and right middle cerebral artery
D. M.	♂	67	.....	.....	Right reacted normally; left eye enucleated	Nystagmus to right	No	No	No	Not determined	Bilateral hemiplegia; bilateral Babinski signs	Aneurysm, basilar artery [illegible] above vertebral arteries, projected to right, compressed chiasm; no subarachnoid hemorrhage
M. T.	♂ Negro	37	.....	.....	Normal	.....	.....	In left fundus	.....	Not determined	Unconscious, blood in spinal fluid	Aneurysm, ruptured, junction of anterior communicating and left anterior cerebral artery
C. P. (Case 13)	♂ Negro	29	Yes	Sympathetic	Right < left	No	No but picture of embolus developed in right eye		No	No gross defect in fields until right eye became blind	Left facial paralysis (central type); paralysis of left 12th nerve; left hemiplegia	Aneurysms visualized (only fairly well) by arteriography
Johns Hopkins Hospital												
J. J. (Case 1)	♂ Negro	28	Not early	Slight	Both fixed to light; late in convergence	Oculomotor nerve palsy, partial	Not at any time	No	No	Right eye blind	None until late in course, when fatal subarachnoid hemorrhage occurred	Aneurysm, junction of anomalous right posterior cerebral and carotid artery
T. G. (Case 3)	♀	40	Early	Yes	Dilated and fixed	Complete oculomotor nerve palsy, right	No	No	No	Paracentral scotoma	Not before operation; postoperative death	Aneurysm, junction of posterior communicating and right internal carotid artery

J. L. H.	♂	43	Yes	24 hours after pain	Right dilated and fixed	Only oculomotor nerve palsies	No	No	No	None demonstrated. Right, 20/40; left, 20/25	None other than oculomotor nerve paralysis, right	Aneurysm, junction of posterior communicating and internal carotid artery, treated surgically; gradual recovery 3d nerve function; internal ophthalmoplegia persisted
Q. D.	♂ Negro	20	Yes	Yes	Right dilated and fixed	Only oculomotor nerve palsies	No	No	No	No. Right, 20/25; left, 20/20	None when seen; subarachnoid hemorrhage 2 or 3 wk. previously	Aneurysm, internal carotid artery anteriorly; 5 mo. later, movements of eye nearly normal; internal ophthalmoplegia persisted
M. D.	♀	34	Yes	No	Both dilated but reacted	No	In both eyes, extensive	No	Blurred disks	Not on gross tests	None other than history of recent epileptiform attacks; died in such an attack; positive blood Wassermann reaction	Aneurysm, ruptured, posterior cerebral artery arising anomalously
W. G. (Case 4)	♂	40	Yes; photophobia	No	Slight irregularity	No	No	No	No	Bitemporal defects	Hypertension; coarctation of aorta; continued hyperpyrexia probably due to involvement of hypothalamus	Aneurysm, attached to anterior communicating artery, seen at operation and verified at autopsy several months later
D. R. (Case 5)	♀	38	Early, right	Yes	Widely dilated and fixed	.....	No	No	No	No	Cranial bruit; persistent internal ophthalmoplegia	Aneurysm, within the cavernous sinus; operation
L. P.	♂	38	Yes	Yes	Right dilated and fixed	.....	Not when diagnosis was made in afternoon; during night, subarachnoid hemorrhage; next morning both eyes showed extensive hemorrhage	Yes	Blurred disks	No. Right, 20/30; left, 20/20	Subarachnoid hemorrhage developed after diagnosis had been made from neightborhood signs; patient died although internal carotid artery was ligated in neck	Aneurysm, junction of right posterior communicating and middle cerebral artery with rupture into internal subarachnoid space and temporal lobe
M. J. R. (Case 7)	♀	18	No	Slight, on right	Normal	Bilateral 6th nerve palsies described; probably brain stem involvement and supranuclear palsies	No	No	No	No	Dizzy spells, unsteady gait, diplopia; regurgitation of fluids; motor aphasia; nystagmus	Aneurysm, attached to left vertebral artery, shoving brain stem to right

Summary of Cases—Continued

Patient	Sex; Race	Age, Yr.	Ocular Symptoms: Pain in Eyes	Ptosis	Status of Pupils	Other Ocular Palsies	Retinal Hemorrhage	Subhyaloid Hemorrhage	Choked Disk	Field Defects; Visual Acuity	Other Neurologic Signs	Operative or Postmortem Observations
H. K. (Case 9)	♂	58	Yes	Developed 10 days later	Dilated and fixed	Right oculomotor nerve palsy	No	No	No	No	Symptoms of subarachnoid hemorrhage; left spastic hemiplegia	Aneurysm, on internal carotid artery anteriorly; exact position not determined
E. H. M. (Case 10)	♂ Negro	50	Yes	Occasionally	Equal and reacted	.....	In each eye	In each eye	Bilateral blurring	Homonymous hemianopia	Questionable ataxia, left arm; sluggish reflexes, right; partial destruction, left posterior clinoid process	Aneurysm (saccular), right middle cerebral artery; arteriovenous (cirsoid) aneurysm, left occipital lobe
J. F. (Case 11)	♂	23	Yes	Yes	Left dilated and fixed	.....	No	No	No	Central scotoma, left field	Pseudomotor lid phenomenon; occasional epileptiform attack	Aneurysm in sinus seen at operation
L. B. (Case 12)	♀	28	Yes	Yes	Left dilated and fixed	Only oculomotor nerve palsies	No	No	No	No	Questionable 7th nerve palsy, left; hyperactive knee jerks; subarachnoid hemorrhage 2 wk. before examination	Intracavernous aneurysm on left; operation followed by loss of vision on left
B. F.	♀	42	.....	On right, incomplete	Right dilated and fixed but reacted in attempted convergence	Diplopia	.....	.....	No	Right, 20/15; left, 20/15—2	Sudden severe pain, right side of head 1 yr. before; frontal pain, 8 mo.; stiff neck	Operation revealed aberrant vessel coming off posterior communicating artery (half as large as internal carotid artery), ran over 3d nerve; internal carotid artery ligated intracranially and in neck
Example of misdirection phenomenon—cf. case 8												
C. S.	♂	36	In left eye and side of head, 9 mo.	Slight, left	Left > right; reacted in convergence	Weakness in adduction and elevation of left eye; diplopia in appropriate fields	No	No	No	No. Right, 20/15; left, 20/15	None other than ocular signs; corneal sensitivity normal	Craniotomy on left; aneurysm protruded anteriorly from cavernous sinus; internal carotid artery ligated intracranially and in neck
M. F.	♀	33	No	Slight	No	No	No	No	Bilateral; 1.5 to 2 D.	No	Loss of consciousness and tonic fit 1 mo. before examination; frequent vomiting; generalized headaches; similar attack 2 wk. later, when use of right arm and leg lost; central facial palsy on right side and inability to move right hand and leg	Craniotomy on right done through pineal approach; hematoma evacuated from third ventricle; autopsy: aneurysm, anterior communicating artery, extending through hypothalamus into third ventricle

F. H.	♀	68	On left side of face, lip, left side of tongue and lower jaw	No ocular symptoms other than pain in eye							Pain in recurring attacks, left side of upper lip for 17 yr.; involved lower jaw, eye, forehead and side of tongue; diagnosed as tic douloureux	Operative section of sensory root, 5th nerve on left; large aneurysm, basilar artery, protruded laterally and squeezed sensory root against tentorium; spinofacial nerve anastomosis performed later
C. R.	♀	59	In frontal area	No	Probably normal but had been dilated with homatropine hydrobromide	No	Hemorrhages at disk and periphery in both eyes, minute	.....	Papilledema: 1.5 D. right, 1 D. left	Fields seemed normal	Drowsy; pulse 40-60; respirations, 12-18; restless; cried out frequently; corneal anesthesia, right; acutely ill only 3 days; had had headache, unlocalized, 2-3 per week for 1 yr.	Bloody fluid found in ventricles; autopsy: subdural hematoma, bilateral; at base aneurysm 3 mm. in diameter on basilar artery at junction of posterior cerebral arteries, intact; aneurysm, anterior communicating artery, ruptured; aneurysm, posteroinferior cerebellar artery, right, unruptured
R. R.	♂	60	Left temporal headaches; pain in left eye 2 weeks	Total left oculomotor nerve paralysis	Left dilated and fixed	Diplopia 2 weeks before admission	No	No	No papilledema	No. Right, 20/20; left, 20/40	Corneal sensitivity normal; proptosis of left eye, 5 mm.	Ligation (partial), left internal carotid artery; later craniotomy on left revealed aneurysm size of pea on under surface of carotid artery; clip placed on it and cautery applied
J. H.	♂	26	No	No	Equal, normal	No	No	No	No	No. Right, 20/15; left, 20/15	At 12, sudden severe headaches; attacks recurred several times; grand mal attacks for 1 yr.; corneal sensitivity normal; roentgen examination showed calcification on left side, suprasellar region; encephalogram negative	Craniotomy on left; aneurysm 0.5 cm. long arose from inner side of internal carotid artery near origin of posterior communicating artery
G. F. C.	♂	34	Pain in right frontal area and about eye	Total left oculomotor nerve paralysis	Right dilated and fixed to light	Diplopia for 2 wk. before examination	Extensive subhyaloid retinal hemorrhages only in right eye	No	No	Right, 20/200; left, 20/15	3 wk. before admission, head cold; severe pain in right side of head for 2½ wk.; diplopia for 2 wk.; spinal puncture had yielded bloody fluid	Operation during period of acute rupture; aneurysm on internal carotid artery below first branch cauterized; patient made uneventful recovery for 24 hr., then had left hemiplegia and became blind in right eye; 1 mo. later had symptoms of subarachnoid hemorrhage and died; probably had another aneurysm which had ruptured

Summary of Cases—Continued

Patient	Sex; Race	Age, Yr.	Ocular Symptoms: Pain in Eyes	Ptosis	Status of Pupils	Other Ocular Palsies	Retinal Hemorrhage	Subhyaloid Hemorrhage	Choked Disk	Field Defects; Visual Acuity	Other Neurologic Signs	Operative or Postmortem Observations
D. Z.	♂	58	No	No	Equal; reacted	External strabismus, left	Bilateral	No	Bilateral	Right, 20/20; left, 20/15	Hypertensive retinitis; blood pressure 154/80; subarachnoid hemorrhage; generalized spacticity with bilateral pyramidal tract signs	Patient dead on arrival at hospital; coarctation of aorta; aneurysms on both middle cerebral and basilar arteries; examination data other than that secured at autopsy based on examination 4 yr. earlier
P. S.	♂	48	Severe headaches, but no pains just around either eye	Right oculomotor nerve paralysis, complete	Right dilated and fixed to light	Corneal hypesthesia	No	No	No	Fields normal ? right, 20/40; left, 20/15	None other than 3d nerve palsy	Ligation of common carotid artery in neck; aneurysm on internal carotid artery; clip placed on internal carotid artery and aneurysm wall cauterized
O. M.	♀ Negro	38	Headache about right eye	Right oculomotor nerve paralysis, 11 days after admission	Right dilated	4th nerve palsy developed several days after 3d nerve palsy; corneal hypesthesia	No	No	No	No. Vision normal	Stiff neck	Subarachnoid hemorrhage; blood in spinal fluid; ligation of internal carotid artery in neck only
M. F.	♀	20	Pain about left eye	Left 3d nerve palsy	Type of Argyll Robertson pupil on left	3d nerve palsy only; hypesthesia, left cornea	No	No	No	Small paracentral scotoma in left field. Right, 20/15; left, 20/15—2	Right hemiplegia before operation; aphasia; cleared before operation	Aneurysm, left internal carotid artery, demonstrated with colloidal thorium dioxide elsewhere; aneurysm removed at operation after ligature of carotid artery intracranially; artery also ligated in neck; after operation, slight aphasia, which cleared; vision in left eye greatly diminished
N. S.	♀	70	Bilateral pain in eyes	No	Pupils normal	No extraocular palsies	No retinal hemorrhages	No	No	.....	Subarachnoid hemorrhage	Bilateral aneurysms demonstrated with colloidal thorium dioxide; left common carotid artery partially occluded; occlusion followed by hemiplegia and aphasia; patient died of bronchopneumonia 1 mo. later; autopsy showed bilateral aneurysms, middle cerebral arteries, aneurysm on basilar artery at distal end and one on right side, anterior communicating artery

SUMMARY AND CONCLUSIONS

A series of cases of saccular aneurysm has been reviewed to exemplify the principles of topical diagnosis. Misdirection of regenerated fibers in the third nerve is recognized in some cases from anomalous movements of the upper eyelid; this lid is elevated when an attempt is made to move the eye by muscles innervated by the third nerve. Misdirection of regenerated fibers also accounts for a type of unilateral Argyll Robertson pupil. Phenomena dependent on denervation may be observed as a result of aneurysm. Those described here are an occasional elevation of the lid in the presence of an apparently complete oculomotor nerve paralysis and contraction of the pupil in the same eye when mecholyl chloride is instilled into the conjunctival sac. Experimental work illustrating the richness of the anastomoses between the branches of the external carotid artery and those of the ophthalmic artery was repeated and enlarged on.

Dr. Walter B. Cannon helped in case 10. Dr. Walter E. Dandy allowed us to use many of his cases and some figures which will later be included in his studies on the neurosurgical aspects of such cases. Mrs. Paul Padget assisted in the preparation of the illustrations.

CORNEAL PENETRATION OF SULFANILAMIDE AND SOME OF ITS DERIVATIVES

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Since the introduction of sulfanilamide and its derivatives in the treatment of ophthalmic infections, a controversy has raged over the efficacy of local therapy. In both experimental and clinical work there has been a marked lack of uniformity in the published results. Investigators have published favorable reports concerning the local use of the drugs in the treatment of corneal ulceration,[1] trachoma,[2] conjunctivitis[3] and various other infective processes.[4] Other investigators[5]

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1. (*a*) Brav, A.: Use of Sulfanilamide in Corneal Infections, Mod. Med. **7**:84, 1939. (*b*) Roggenkämper: Hornhautulkus und Prontosil, Klin. Monatsbl. f. Augenh. **103**:211, 1939. (*c*) Glover, L. P.: Some Uses of Sulfanilamide in Ophthalmology, Am. J. Ophth. **22**:180, 1939. (*d*) Paton, R. T.: Subconjunctival Injections of Neoprontosil in Treatment of Ocular Infections, Arch. Ophth. **22**: 377 (Sept.) 1939.

2. Rambo, V. C.: The Use of Sulfanilamide in Trachoma, Proc. All-India Ophth. Soc. **6**:193, 1938; abstracted, Am. J. Ophth. **24**:90, 1940. Cosgrove, K. W.: The Local Use of Sulfanilamide in Trachoma: A Preliminary Report, ibid. **23**:911, 1940. Vajda, G.: Chemotherapy, Orvosi hetil. **82**:142, 1938; cited by Szinegh, B.: Beiträge zur Chemotherapie des Trachoms, Arch. f. Ophth. **141**:109, 1939. Brav.[1a] Paton.[1d]

3. Panneton, P.: Local Treatment of Gonorrheal Conjunctivitis with Sulfanilamide Powder, Am. J. Ophth. **24**:314, 1941. Mullen, C. R.: Treatment of Gonorrheal Diseases of the Eye with Sulfanilamide, Arch. Ophth. **25**:655 (April) 1941. Breuns, E.: Zur Chemotherapie der Gonoblennorrhoe der Neugeborenen (Ein Beitrag zur ortlichen Anwendung der Albuzid), Klin. Monatsbl. f. Augenh. **105**: 430, 1940. Thygeson, P.: Personal communication to S. R. Gifford, 1941. Allen, J. H., in discussion on Thygeson, P.: Treatment of Inclusion Conjunctivitis with Sulfanilamide, Arch. Ophth. **25**:217 (Feb.) 1941. Friedman, B., in discussion on Paton.[1d] Glover.[1e]

4. Heinz, K.: Subkonjunktivale Injektion von Prontosil solubile (Bayer) bei exogener und endogener Infektion des Augeninnern, Ztschr. f. Augenh. **95**:365, 1938. Paton.[1d]

5. Meoni, M.: La chemioterapia sulfamidica nelle affezioni oculari, Arch. di ottal. **46**:163, 1939. Smith, J. E.; Julianelle, L. A., and Gamet, J. H.: Sulfonamide

have expressed the opinion that local treatment is a valuable but secondary adjunct to oral medication. Guyton [6] reported that local application of 5 per cent sulfanilamide ointment had no effect in 18 cases of catarrhal conjunctivitis although encouraging results were obtained in treating infected corneal ulcers. No significant beneficial results were obtained from similar applications of sulfanilamide or sulfapyridine in eyes infected with Haemophilus influenzae.[7] The therapeutic action of dimethyldisulfanilamide (N,[1] N [1]-dimethyl-N [4]-sulfanilylsulfanilamide) employed as a 5 per cent ointment in 4 cases of gonorrheal conjunctivitis was unimpressive. Three to five weeks elapsed before the conjunctival sac was freed from gonococci.[8] Mengel [9] reported that less than 0.1 mg. of sulfanilamide per hundred cubic centimeters was present in the aqueous humor after instillation of a saturated aqueous solution of the drug. Lou and P'an,[10] on the other hand, found an average of 2.6 mg. per hundred cubic centimeters after local instillation of a warmed 1 per cent solution of sulfanilamide and 22.3 mg. per hundred cubic centimeters when the powdered drug was employed.

Experimentally the results are equally confusing. In dogs Bellows and Chinn [11] found no sulfanilamide in the aqueous within two hours after the drug had been dusted on the cornea and the conjunctiva. In rabbits Guyton [6] reported no absorption of azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonate) after local instillation of 2.5 per cent solution every ten minutes for four hours. With sulfanilamide similarly applied, a concentration of 4.8 mg. per hundred cubic centimeters was attained. Pinkhof [12] found

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Therapy of Trachoma, Am. J. Ophth. **24**:174, 1941. Sie Boen Lian: Prontosil in Treatment of Trachoma, Geneesk. tijdschr. v. Nederl.-Indië **78**:1058, 1938; cited by Szinegh.[2]

6. Guyton, J. S.: Local Use of Sulfanilamide Compounds in Eye, Am. J. Ophth. **24**:292, 1941.

7. Guyton, J. S.: Effects of Sulfanilamide and Sulfapyridine on the Koch-Weeks Bacillus (Haemophilus Influenzae), Arch. Ophth. **23**:1243 (June) 1940.

8. Kattiofsky, W.: Erfahrungen über die Wirksamkeit der Sulfanilamide bei gonorrhoischen Augenkrankungen, Klin. Monatsbl. f. Augenh. **103**:214, 1939.

9. Mengel, W. G.: Determination of Sulfanilamide in Aqueous and Vitreous After Conjunctival and Oral Administration, Arch. Ophth. **22**:406 (Sept.) 1939; The Determination of Sulfanilamide in Aqueous and Vitreous Following Administration, Am. J. Ophth. **23**:696, 1940.

10. Lou, T. H., and P'an, S. Y.: Concentration of Sulfanilamide in the Aqueous Humor of Human Eyes with Special Reference to Local Application, Chinese M. J. **58**:167, 1940.

11. Bellows, J. G., and Chinn, H.: The Distribution of Sulfanilamide in the Eye, J. A. M. A. **112**:2023 (May 20) 1939.

12. Pinkhof, J.: The Content of Sulfanilamido-Pyridine (M. & B. 693) in the Ocular Fluids of Rabbits After Administration of the Drug, Ophthalmologica **97**: 357, 1939.

no intraocular absorption of sulfapyridine after application of the drug into the conjunctival sac. On the other hand, one hour after 100 mg. of powdered sulfanilamide had been applied into the conjunctival sac of a rabbit, P'an [13] showed the aqueous humor to have over 50 mg. per hundred cubic centimeters and significant quantities to be present in every tissue or fluid of the eye. P'an kept the treated eye closed by means of a clamp. Guyton [6] investigated the corneal absorption of sulfanilamide and sulfapyridine prepared in ointment form and found that considerable sulfanilamide but only traces of sulfapyridine penetrated the cornea.

In order to gain more information on this controversial subject we have investigated the corneal absorption of sulfanilamide and various derivatives used therapeutically. Both the dog and the rabbit have been used in determining whether there is any significant species difference.

EXPERIMENTS

Ointments containing sulfanilamide,[14] sulfapyridine,[15] sulfathiazole [16] and sulfadiazine [17] were prepared according to the directions of Guyton for "ointment 8." [4] This ointment had been reported by him to be the most effective of all those tested for the absorption of sulfanilamide. A bland preparation resulted with sulfanilamide and with sulfathiazole. The lower solubility of sulfapyridine and of sulfadiazine caused the ointments made with these drugs to be less satisfactory. The ointments were applied to the eyes of rabbits or dogs at thirty minute intervals for six hours. Care was taken to insure complete distribution over the corneal surface after each application. The rabbits remained conscious, while the dogs were kept under pentobarbital anesthesia. At the end of the prescribed period the eyes were thoroughly washed and the aqueous removed. The concentration of the sulfanilamide derivatives was determined in the manner described earlier.[18] The accompanying table shows the relative absorption in the dog and in the rabbit of the drugs employed.

As is evident from this table, the local absorption of sulfanilamide was marked in the rabbit, averaging more than five times that in the dog. We found that similar concentrations could be obtained in the

13. P'an, S. Y.: Distribution of Sulfanilamide in the Ocular Fluids and Tissues After Local Application, Proc. Soc. Exper. Biol. & Med. **46**:31, 1941.

14. Supplied by Merck & Co., Inc., Rahway, N. J.

15. Sulfapyridine is 2-(paraaminobenzenesulfonamido)-pyridine. It was supplied by Merck & Co., Inc., Rahway, N. J.

16. Sulfathiazole is 2-(paraaminobenzenesulfonamido)-thiazole.

17. Sulfadiazine is 2-(paraaminobenzenesulfonamido)-pyrimidine. It was supplied by Lederle Laboratories, Inc., Pearl River, N. Y.

18. Bellows, J. G., and Chinn, H.: Penetration of Sulfathiazole in the Eye, Arch. Ophth. **25**:294 (Feb.) 1941.

aqueous after two hours of treatment. The average value compares very well with that obtained by Guyton [6] after four hours. The penetration of the other drugs was slight both in the dog and in the rabbit, although a higher value was found for the aqueous of the latter animal in every instance. The concentrations of these compounds in the aqueous of the dog after oral administration are listed for comparative purposes. Irritative manifestations were negligible.

An even more marked species difference was noted when sulfanilamide powder was used instead of the ointment. One hundred milligrams of sulfanilamide was placed in the conjunctival sac of a rabbit and the lids approximated and clamped. At the end of two hours, after careful irrigation of the surface, aqueous was aspirated and the sulfanilamide

Concentration of Sulfanilamide and Its Derivatives in the Aqueous Humor After Oral and After Local Administration

	Sulfanilamide, Mg. per 100 Cc.	Sulfapyridine, Mg. per 100 Cc.	Sulfathiazole, Mg. per 100 Cc.	Sulfadiazine, Mg. per 100 Cc.
Dog				
Oral *	11.6[11]	5.4 †	0.4[18]	...
Local ‡	6.1	1.6	0.3	0.7
Rabbit				
Oral	2.4 §	0.6 ‖ 4.1 ¶	...	...
Local ‡	31.1	2.3	2.6	3.0

* Six hours after the ingestion of 200 mg. of drug per kilogram of body weight.

† Chinn, H., and Bellows, J. G.: J. Lab. & Clin. Med. **25**: 735, 1940.

‡ Applied in an ointment every half hour for six hours.

§ Single value obtained for a rabbit given 0.6 Gm. at 4 p. m. and again at 10 p. m. and killed the next morning (Rambo, V. C.: Am. J. Ophth. **21**: 739, 1938).

‖ One-tenth gram of drug per kilogram of body weight given two and a half to seven hours (average two and eight-tenths hours) before removal of the aqueous.[12]

¶ Approximately 0.6 Gm. of drug per kilogram of body weight given four and one-half to ten hours (average, seven and one-tenth hours) before removal of the aqueous.[20]

determined. The dogs were similarly treated except that 200 mg. of the drug was applied and the animal remained anesthetized for the duration of the experiment. The average value for sulfanilamide in the aqueous of the dog was 6.6 mg. per hundred cubic centimeters, whereas the aqueous of the rabbit showed almost fifteen times as much (88 mg.). In most eyes there was a slight but definite staining of the cornea, and in many eyes chemosis was observed. This is in harmony with the findings of Lou and P'an.[10] The corneal involvement was superficial and could be seen macroscopically. Such injury would not be distinguishable histologically, which may account for the negative microscopic observations by P'an.[13]

COMMENT

The results reported here indicate that the clinical use of sulfanilamide locally in the treatment of intraocular infections has experimental justification but that the local use of its derivatives is of questionable value. In the dog sulfanilamide appeared in the aqueous humor in rela-

tively high concentrations, while sulfapyridine, sulfathiazole and sulfadiazine penetrated the cornea to a more limited extent. Even with sulfanilamide the concentration was only 6.6 mg. per hundred cubic centimeters, whereas after oral administration a maximum concentration of 11.6 mg. per hundred cubic centimeters was obtained. Studies on the penetration of sulfadiazine into ocular tissues [19] have not yet appeared; so a comparison of oral and of local administration of this compound cannot be made. The amount of sulfathiazole reaching the aqueous humor by either route is negligible, whereas with sulfapyridine approximately 5 mg. per hundred cubic centimeters appeared in the aqueous after the oral ingestion of 200 mg. per kilogram of body weight and only 1.6 mg. after local application. The rabbit's cornea is far more permeable to these compounds than is the dog's. Whether the absorption by the cornea in man approaches more closely that in the dog or that in the rabbit unfortunately has not been determined. The finding by Lou and P'an [10] of a concentration of sulfanilamide in the aqueous of man of 22 mg. per hundred cubic centimeters after local application would place the permeability between that of the dog and that of the rabbit. Friede [19a] reported the thickness of the central part of man's cornea as 0.9 mm., that of the rabbit's cornea as 0.8 mm. and that of the dog's cornea as 0.9 mm. The thickness at the periphery was even greater in man. However, the thickness would be only one factor involved in the permeability of the cornea.

The extremely high corneal penetration obtained in rabbits when sulfanilamide was powdered directly into the conjunctival sac was surprising. The concentrations were higher in the rabbit's eye than those following the use of an ointment. The slight damage to the corneal epithelium might have increased its permeability to the drug.

In summary, it would seem from the results of our investigation and from the clinical and laboratory reports of others that in most cases the combined oral and local administration of these drugs would be the most effective procedure. If the efficacy of the drug is dependent only on its concentration, the local application of sulfanilamide and its derivatives might be adequate, particularly for minor external ocular infections. The high values reported by P'an [13] for the corneal concentration after local application of sulfanilamide and the strong adsorptive power

19. Since this paper was prepared, the penetration of sulfadiazine into the aqueous has been reported to approximate that of sulfapyridine, in Scheie, H. G., and Souders, B. F.: Penetration of Sulfanilamide and Its Derivatives into Aqueous Humor of Eye, Arch. Ophth. **25**:1025 (June) 1941.

19a. Friede, R.: Vergleichende Studien zur Grosse der tierischen und menschlichen Hornhaut mit besonderer Berücksichtigung der menschlichen Megalocornea, Arch. f. Ophth. **131**:1, 1934.

of the cornea for this drug [20] suggest especial applicability for corneal infections. However, most reliance should still be placed on oral administration in the treatment of virulent and progressive external infective diseases and especially in the treatment of intraocular infections. This is even more true for the use of sulfapyridine, sulfathiazole and sulfadiazine than it is for the use of sulfanilamide, since the corneal penetration of the former derivatives is far less than that of the simpler sulfanilamide molecule.

SUMMARY

1. The concentrations of sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine in the aqueous humor were determined after the corneal application of the respective drug in ointment form. It was found that sulfanilamide readily penetrated the normal cornea of the rabbit. The cornea of the dog was more impermeable, the amount reaching the aqueous being only 20 per cent of that in the rabbit. The other drugs penetrated the cornea only slightly, with more appearing in the rabbit's aqueous in every instance than in the aqueous of the dog.

2. The powdered form of sulfanilamide applied in the conjunctival sac of the rabbit produced a concentration in the aqueous higher than that produced by the sulfanilamide ointment. The value was approximately fifteen times that for the concentration in the aqueous of the dog similarly treated.

3. A slight staining reaction of the cornea was noted with the powdered sulfanilamide and in some instances chemosis as well.

The clinical implications of these findings are discussed.

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20. Meyer, K.; Bloch, H. S., and Chamberlain, W. P., Jr.: Distribution of Sulfapyridine Between Blood, Aqueous Humor and Cornea, Am. J. Ophth. **24**:60, 1941.

TREATMENT OF RETINOBLASTOMA (RETINAL GLIOMA) SURGICALLY AND BY IRRADIATION

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In 1936, we published a preliminary report [1] on the treatment of bilateral retinoblastoma by a technic of fractionated irradiation which had not previously been used for this form of cancer. That report was based on 6 cases of bilateral growths in which one eye had been removed and the other irradiated in an attempt to control the growth and conserve vision. One of the purposes of this communication is to give the follow-up to date in these 6 cases and to submit preliminary data on 4 more recent cases of bilateral retinoblastoma in which the treatment was similar.

In the present report we shall also discuss the other clinical forms and stages of retinoblastoma (unilateral tumors, advanced bilateral growths with the vision irreparably destroyed by the time of admission, postoperative recurrent retinoblastoma and widely disseminated retinoblastoma), in the treatment of which radiation therapy as a means of conserving vision is not applicable. Because pertinent data were lacking in the histories of patients treated at the Memorial Hospital for the Treatment of Cancer and Allied Diseases between the years 1916 and 1929 inclusive, these cases are briefly summarized collectively in table 1. Individual case histories of patients treated between the years 1930 and 1940 inclusive are given in tables 2, 3, 4 and 5.

Read in part at the Annual Session of the American Academy of Ophthalmology and Otolaryngology, Cleveland, Oct. 6, 1940. Since that time there have been no changes in the cases presented except those shown in the footnotes to Table 3.

1. Martin, H. E., and Reese, A. B.: Treatment of Retinal Gliomas by the Fractionated or Divided Dose Principle of Roentgen Radiation, Arch. Ophth. **16**:733-761 (Nov.) 1936.

SELECTION OF TREATMENT FOR RETINOBLASTOMA

An ideal method of treatment for retinoblastoma would eradicate the growth and leave normal vision in both eyes. Unfortunately, such an ideal has so far been impossible of attainment. In the first place, a malignant tumor of the retina, even though small, cannot be removed surgically without enucleation of the eye. Secondly, whether the growth is unilateral or bilateral, the disease is invariably so far advanced as to have irreparably destroyed vision in at least one eye before there are sufficient objective or subjective symptoms to permit of a diagnosis.

If the growth is unilateral, there can be no question but that the safest plan is to enucleate one eye immediately, being content with the

TABLE 1.—*Data on Patients with Retinoblastoma Treated at the Memorial Hospital for the Treatment of Cancer and Allied Diseases 1916 to 1929 Inclusive*

	Number of Patients	Male	Female	Left Eye	Right Eye	Treatment: Irradiation	Treatment: Enucleation	Treatment: Combination	Cataract	Glaucoma	Metastasis	Outcome*
Group 1: With primary unilateral retinoblastomas	7	3	4	2	5	..	1	6	..	1	1	1 DOD 2 NED 2 L with D 2 L no D
Group 2: With bilateral tumors	16	8	8	..	..	4	..	12	1	..	3	8 DOD 2 NED 5 L with D 1 L no D
Group 3: A, with recurrence after enucleation	5	2	3	3	2	4	..	1	..	..	5	4 DOD 1 L with D
B, with residual tumor after enucleation	3	1	2	3	..	3	..	..	..	..	1	1 DOD 2 L no D

* DOD, dead of disease; NED, no evidence of disease; L with D, lost with disease present; L no D, lost with no disease present.

remaining monocular vision. If the disease is bilateral, the best that can be hoped for is to enucleate the eye with the more advanced involvement and to conserve vision, if possible, in the other eye by radiation therapy.

When the involvement of both eyes is so extensive that no vision in either can be conserved by any means, irradiation has no practical advantage over enucleation of both eyes, since in either case total blindness is inevitable. As a matter of fact, radiation treatment is contraindicated in cases of such advanced retinoblastoma, since even a moderate delay in the complete eradication of the growth unquestionably increases the danger of wide dissemination. The cosmetic appearance following enucleation of the eye is superior to that which follows the complete sterilization of an advanced growth by irradiation. In brief, the only

purposes for which irradiation is indicated in the treatment of retinoblastoma are (1) to treat early growths in an attempt to conserve vision in one eye and (2) to treat residual or postoperative recurrent tumors.

The selection of the method of treatment in a given case of bilateral retinoblastma is somewhat empiric and may depend largely on the past experience and the success or failure in similar cases. We believe that if bilateral growths are too far advanced to permit of any reasonable chance of conserving vision in either eye by irradiation, bilateral enucleation should be done immediately. In our previous report we expressed what would probably even now be the general medical and lay opinion on this subject, i. e. that the removal of both eyes, the child being immediately blinded thereby, would not be justified even though it saved life. Since that time, however, after observing the terminal course in 2 patients, we have altered this opinion. One of the patients (patient 22, fig. 1) was considered incurable on admission, and the treatment policy originally decided on was that of noli me tangere. As the disease progressed, however, the primary tumors produced painful bulky enlargements of the globes which protruded between the lids, with corneal ulceration, perforation of the eyes and sepsis and with so much local pain that we were forced to remove first one and then the other eye for palliative purposes several months before death. Leaving the eyes in place until their removal was obligatory accomplished no useful purpose and only permitted the certain wide dissemination of the growth when life might possibly have been saved by immediate bilateral enucleation. The second patient, whom we saw only in consultation on three occasions, was treated elsewhere by enucleation of one eye and irradiation of the other. Irradiation failed to control the tumor in the eye not enucleated, and when we last saw the child, the growth was obviously extending and there was little remaining vision. At that time we advised enucleation of the remaining eye in an attempt to save life, since the child would soon be blind in any case; the eye had already begun to be painful and there was as yet no evidence that the disease had extended beyond the globe. The parents refused to permit the operation, and the child died about three months later, the sole cause possibly being the local effects of the tumor.

It is surely more humane to strive for a complete cure of the disease and survival, even with blindness, through a normal span of life than to select for the child the doubtful privilege of a few weeks of rapidly diminishing vision followed by inevitable complete blindness and a painful death after several months of suffering. We had to settle this question recently in the case of a child (patient 23) with bilateral retinoblastoma and only slight vision in one eye. After a frank discussion with the parents, in which we reviewed with them the clinical his-

TABLE 2.—*Data on 4 Cases of Unilateral Retinoblastoma*

TABLE 2.—*Data on 4 Cases of Unilateral Retinoblastoma*

Case No.; Age; Date First Seen at Memorial Hospital	Clinical Findings	Period of Irradiation	Course	Glaucoma	Cataract	Date of Enucleation; Pathologic Observations	Metastases	Present Status	Autopsy
1 2½ yr. Jan. 1936	Right Eye: Negative Left Eye: Uniform, somewhat elevated involvement of entire retina; considerable vascularity; 1 mass, nasal and downward, extending from most peripheral portion to posterior pole, no calcium, vascular; 1 mass, continuous with other, extending to vertical meridian, much less elevated, less vascular, calcium; disk obscured by tumor tissue	Left eye, 6 mo.	Steady regression of lesion	April 1936, tension 15; Aug. 1936, tension 45; trephine operation	Sept. 1936, no cataractous changes	Left Eye, Oct. 1936: Entire retina detached and occupied by tumor which is necrotic below with calcium deposits, and viable above, with perivascular growth; growths along choroidal surface; no extension into optic nerve; some lens changes	None	No evidence of disease 3½ yr. after radiation treatment	
2 (fig. 2) 3 yr. July 1936	Left Eye: Negative Right Eye: Large whitish growth involving entire globe except nasal-superior portion	Right eye, 4 mo. 11 days	Regression of lesion for 2 mo.; then detachment of retina, temporal half	Dec. 1936; acute glaucoma	Dec. 1936, lens cataractous	Right Eye, Dec. 1936: Tumor fills choroid and ciliary body from iris to posterior pole; tumor cells extend through sclera; areas of necrosis in tumor mass; most of cells pyknotic; tendency to perivascular growth; retina detached over tumor but replaced at one area by new growth; smaller tumor lesion in choroid near ora serrata on opposite side; no extension through nerve	March 1937, left parietal region; then left femur, left frontal region, left zygoma, left axilla, right mandible, left occipital region, right orbital socket, right side of neck; these sites received radiation	Died 14 mo. after start of radiation treatment	No evidence of local disease; generalized subperiosteal metastases; metastases to hilar nodes; liver, subcutaneous tissue of thorax; congestion of kidneys and spleen; roentgenograms of skeleton showed extensive involvement of pelvis, femurs, tibias and humeri
3* 4 yr. Feb. 1936	Left Eye: Negative Right Eye: Enucleated 4 mo. before elsewhere; no evidence of local tumor (see "metastases")	No radiation given to socket	No evidence of local tumor	.....	.....	.....	Feb. 1936: Masses in right preauricular region, left superior orbital region extending into orbit with ptosis of upper lid, bilateral enlargement of cervical lymph nodes, swelling of right arm and hand and of left tibia; these sites received radiation for 3 mo.	Died 7 mo. after enucleation and 3 mo. after start of radiation treatment	Multiple metastases to bones and cervical and retroperitoneal lymph nodes
4 4 yr. Jan. 1931	Right Eye: Negative Left Eye: Enucleation 2 wk. previously; exenteration of orbital cavity shortly afterward	Prophylactic irradiation	No evidence of local tumor	.....	.....	.....	None	No evidence of disease 10 yr. after exenteration	

* A case of distal metastases without local recurrence in orbit.

TABLE 3.—*Data on 10 Cases of Bilateral Retinoblastoma Treated by the Fractionated, or the Divided Dose, Principle of Roentgen Irradiation*

Case No.; Age; Date First Seen at Memorial Hospital	Clinical Findings	Period of Irradiation	Course	Glaucoma	Cataract	Date of Enucleation; Pathologic Observations on Eyes Receiving Radiation	Metastases	Present Status	Autopsy
5 (fig. 14) 9 mo. Feb. 1933	Right Eye: Enucleation July 1932; elsewhere, with no implant; pathologic diagnosis, retinoblastoma Left Eye: Mass in macular region extending to disk; 8 to 9 D. elevation	Left eye, 16 mo.	Steady regression of lesion	Not present	May 1938: Very small localized opacity posterior part of the lens cortex temporally; no progression to Nov. 1940	.....	None	Lesion arrested; vision 20/25; good general health; attends regular school (fig. 14)	.....
6* 5 yr. Aug. 1933	Left Eye: Enucleation with no implant; pathologic diagnosis, retinoblastoma Right Eye: Mass at equator, from 3 to 5 o'clock; 7 to 8 D. elevation; 4 disk diameters across	Right eye, 20 mo.	Steady regression of lesion	Not present	Jan. 1937: Posterior polar opacity which progressed until Feb. 1940, when, vision being 20/200, needling was done, followed 1 wk. later by linear extraction	.....	None	Lesion arrested; vision 20/100 — 1 (reduced vision due to macular changes secondary to either growth or irradiation); good general health; attends school	.....
7 14 mo. Dec. 1934	Left Eye: Enucleation with no implant; pathologic diagnosis, retinoblastoma Right Eye: 1 mass at nasal part of disk margin, peripherally, 3 disk diameters across, 5 D. elevation, surface blood vessels; 1 mass, small budlike, directly above	Right eye, 15 mo.	Steady regression of lesion seen as long as interior of eye could be observed	Right Eye: Jan. 1936: Secondary glaucoma with steamy cornea, also vascularized pannus, trephine operation April 1936: Tension 50, trephine operation	Sept. 1936: Lens completely cataractous	.....	None	Lesion arrested; but globe shrunken; small vascularized cornea; xerotic conjunctiva; some symblepharon; patient blind but in good general health	.....
8 11 mo. March 1935	Right Eye: 1 mass in macular region, 4 D. elevation, surface blood vessels; 1 mass nasally above horizontal meridian Left Eye: Buphthalmic; vitreous filled with mass; surface blood vessels; tension 48	Right eye, 15 mo. Left eye, 3 mo.	Right Eye: Steady regression of lesion as long as interior of eye could be seen Left Eye: After 2 wk., hyphemia; in 2 mo., globe atrophic	Right Eye: June 1936, secondary glaucoma with steamy cornea, also vascularized pannus Aug. 1936: Tension 35, trephine operation Nov. 1936: Tension 50, trephine operation	Jan. 1937: Lens cataractous	Left Eye: 1935: Globe phthisical; retinal elements not recognizable; vitreous partially filled with necrotic tumor tissue containing many foci of calcium; no extension into nerve or through sclera	March 1937, 4 cm. ovoid mass subcutaneous tissue right submaxillary region; complete regression after roentgen irradiation	Right Eye: Tumor arrested but globe phthisical; xerotic conjunctiva and unusual piling up of keratin on cornea in form of conical protuberance between palpebral apertures for 10 to 12 mm., which finally falls off only to accumulate again; blind but in good general health	.....
9	Right Eye: 1 large	Right eye	Regression sat-	Not present	No cataractous	.....	Unknown	Died 1 yr. 10 mo. after first observa-	Permission for autopsy not ob-

9 17 mo. May 1935	Right Eye: 1 large bullous mass below disk, surface blood vessels; 1 small nodule 4 disk diameters temporal to disk Left Eye: Enucleation, with no implant; pathologic diagnosis, retinoblastoma	Right eye 14 mo.	Regression satisfactory for 5 mo.; then lesion below disk increased in size, first concealing disk, then spreading into and under retina; after 1½ yr. of treatment most of vitreous cavity occupied; implantation growths on iris; tumor thought to have invaded choroid	Not present	No cataractous changes	.....	Unknown	Died 1 yr. 10 mo. after first observation and start of treatment	Permission for autopsy not obtained
10 (figs. 8, 9 and 10) 10 mo. Sept. 1935	Right Eye: 1 mass nasal to disk, horizontal meridian, 4 disk diameters in size, 4 D. elevation, surface blood vessels; 1 mass half size directly below; tension 35 Left Eye: 1 mass in macular region from disk margin to periphery; 6 D. elevation, surface blood vessels; 1 mass nasally at horizontal meridian, 2 disk diameters in size; tension 30	Right eye, 8 mo. Left eye, 8 mo.	Right Eye: Steady regression of lesion Left Eye: Regression satisfactory for 7 mo.; then retina appeared detached around site of temporal lesion; gradually more elevated and bullous-like with tumor area mounted on its surface; tumor thought to have invaded choroid	May 1936: Secondary glaucoma	No cataractous changes	Left Eye, June 1936: Retina detached; on temporal side replaced by necrotic tumor tissue with calcium foci; small areas viable tumor about blood vessels; extension of tumor into nerve for short distance posterior to lamina cribrosa but operative section free; no extension through sclera; many implantation growths on choroid; on temporal side, beneath primary retinal site, flat extension of tumor into choroid from disk to point past equator, actively growing	Oct. 1936: Mass in left orbit, irradiated; roentgenograms showed left ethmoid, nasal wall and floor of orbit extensively involved; bones of skeleton not involved Later, mass left side hard palate and mandible Later, right and left cervical glands palpable	Died 1 yr. 10 mo. after first seen	Recurrent retinoblastoma of left orbit with extension to nasal cavity and bones, to right maxilla and mandible and adjacent bones, to cranial cavity via nasal cavity and cribriform lamina and to opposite orbit from nasal cavity Right Eye: In retina, nasal to disk, slightly above horizontal meridian, 4 disk diameters away, mass 2 to 3 disk diameters wide, 1½ disk diameters high, mostly dense, solid calcium and necrotic tissue with clear areas of absorption; flat tumor in choroid beneath retinal lesion, extending to disk and several disk diameters around it; choroidal tumor extended through posterior emissaria to external scleral surface; tumor cells identifiable as far anteriorly as limbus; tumor in nerve head but not as far as lamina cribrosa

TABLE 3.—*Data on 10 Cases of Bilateral Retinoblastoma Treated by the Fractionated, or the Divided Dose, Principle of Roentgen Irradiation—Continued*

Case No.; Age; Date First Seen at Memorial Hospital	Clinical Findings	Period of Irradiation	Course	Glaucoma	Cataract	Date of Enucleation; Pathologic Observations on Eyes Receiving Radiation	Metastases	Present Status	Autopsy
11 3 mo. Oct. 1937	Right Eye: 1 mass, nasal to and above disk 2 to 3 disk diameters wide, 2 D. high, 1 surface blood vessel; 1 mass (smaller) temporally above macula Left Eye: Enuclation with no implant; pathologic diagnosis, retinoblastoma	Right eye, 5 mo.	Right Eye: Steady regression of lesion as long as interior of eye could be seen (4½ mo.); then pannus of cornea and corneal vascularization developed	Right Eye: Secondary glaucoma; March 1939, trephine operation; March 1940, trephine operation; May 1940, iridotasis operation	Lens became cataractous after atrophy of globe	.....	None	Right Eye: Tumor arrested but cornea completely opaque with marked vascularity; xerosis of cornea and conjunctiva; blind but in good general health	
12 2 mo. June 1938	Right Eye: Enucleation with no implant; pathologic diagnosis, retinoblastoma Left Eye: Temporally, horizontal meridian, 3 to 4 disk diameters from disk, mass 3 by 4 disk diameters, 4 D. high	Left eye, 2½ mo	Complete disappearance of tumor; only some calcium granules remained	Not present	No lens changes	.....	None	Apparently normal vision and good general health	
13† (fig. 13) 3 yr. June 1939	Right Eye: Enucleation with no implant; pathologic diagnosis, retinoblastoma Left Eye: Peripherally, nasal, on horizontal meridian, from near equator to limit of visibility; surface vessels	Left eye, 4 mo.	Left Eye: Steady regression	Not present	No lens changes	.....	None	Left Eye: Tumor arrested; vision 20/20; good general health	
14‡ 3 yr. May 1940	Right Eye: Tumor mass occupied entire nasal portion of fundus Left Eye: Enucleated without implant; pathologic diagnosis, retinoblastoma	Right eye, 4 mo.	Steady regression of tumor for 4 mo.	Not present	No lens changes	.....	None	Right Eye: Tumor appears arrested; vision, counts fingers at 20 feet	

* Case 6.—In October 1940 exophthalmos of the right eye developed. A biopsy specimen was taken from the orbit, considerable soft friable tissue and a defect in the lateral wall of the orbit being encountered. From microscopic sections of the tissue a diagnosis of rhabdomyosarcoma was made. With the ophthalmoscope no change was noted at the site of the lesion in the retina. The patient died in October 1941. Permission for an autopsy was obtained, and the right eye was secured for microscopic examination. The autopsy indicated that the rhabdomyosarcoma probably arose from the right temporal muscle, with secondary orbital extension through the lateral bony wall. Death was caused by intracranial extension. The examination of the enucleated eye showed no activity at the site of the retinal lesion.

† Case 13.—In November 1941 secondary glaucoma developed in the right eye, which necessitated a modified Lagrange operation. The patient is now in the hospital. Before the onset of the glaucoma there were some macular hemorrhages and residual edema, which reduced the vision to 20/100. The area involved by the retinoblastoma has shown no sign of active growth.

‡ Case 14.—Because of the extensive involvement of the fundus with retinoblastoma, it could not be determined whether or not the irradiation had controlled the growth, and therefore in September 1941 the right eye was enucleated.

tory in similar cases, the unanimous verdict was that both eyes should be removed immediately. Since bilateral enucleation there has been no recurrence of the growths up to the present time, and the child, otherwise healthy, is attending a school for the blind.

Is it not presumptuous for any one—parent, physician or lay committee—to decide arbitrarily for the child that death is preferable to life without eyesight? It is a curious fact that in those cases which have attracted so much attention in the public press it has never even been

Fig. 1 (case 22).—Terminal stages of untreated bilateral retinoblastoma. Both globes are buphthalmic and proptosed; the proptosis is so marked on the right side that there are corneal ulceration and some necrosis of the exposed tissue. The left cornea is steamy, but tumor tissue can be seen in the anterior chamber. A few days after this picture was taken it was necessary to enucleate the right eye for hygienic reasons and to relieve the patient of constant pain. A month later the left eye was enucleated for the same reasons. This case illustrates the fact that in hopeless cases of bilateral retinoblastoma, as soon as permission can be obtained bilateral enucleation should be performed in order to prevent unnecessary suffering which will eventually compel enucleation of the eyes with no hope of saving life, since by that time the disease will have become widely disseminated.

suggested that this question be referred to a committee of adults who have themselves been blind since childhood. Such a committee probably

† Case 14.—Because of the extensive involvement of the fundus with retinoblastoma, it could not be determined whether or not the irradiation had controlled the growth, and therefore in September 1941 the right eye was enucleated.

TABLE 4.—*Data on 7 Cases of Recurrent or Residual Retinoblastoma in Orbit Treated with Irradiation After Enucleation*

Case No., Age	Enucleation	Recurrence or Residual Tumor in Orbit	Course Following Irradiation	Metastases *	Outcome	Autopsy
15 3½ yr.	Right eye: Glass ball implant	Evident after 3½ mo.	Disappearance of tumor in orbit	4 mo. later: pain in both legs and chain of small nodes palpable in right cervical region; roentgenograms showed involvement of shaft of both humeri, upper end of right fibula and tibia and each scapula	Died 1 yr. after enucleation and 9½ mo. after recurrence and beginning of treatment	Metastasis to pancreatic nodes, acute interstitial pancreatitis; extension of tumor into left chiasm and left optic nerve; renal metastasis; epicardial hemorrhagic area failed to show tumor in section but a metastasis probably present, nearly occluding a vessel
16 5 yr.	Left eye: No implant; pathologic observations: entire globe filled with tumor; rupture through limbus with growth along external scleral surface almost to equator; choroid invaded everywhere except for short distance at equator; optic nerve invaded to lamina cribrosa; no invasion through emissaria	Evident after 5 mo.; also numerous soft freely movable nodes palpable in cervical region, especially on left side; 1 large node beneath angle of right mandible	Complete regression	See note under "Recurrence or Residual Tumor in Orbit"	No evidence of disease 1 yr. 9 mo. after enucleation and 14 mo. after recurrence	
17 2½ yr.	Left eye: No implant; pathologic observations: extensive lesion invading optic nerve, completely replacing nerve tissue and extending into intervaginal space; choroidal extension; operative section not free of tumor tissue	Evident after 3 wk.	Disappearance of mass in orbit	2 mo. later: headache, listless, vomiting; right eye appeared blind; 1 mo. later: coma, convulsions	Died 5 mo. after enucleation and 4 mo. after recurrence was noted	Invasion of brain with tumor; internal hydrocephalus; subperiosteal metastasis to calvarium
18 17 mo.	Left eye: No implant	1 mo. (case referred for prophylactic irradiation); 2 mo. later, firm mass palpable in orbit	Disappearance of mass	4 mo. later: pain in back and walking difficult; prominence over left sacral region (roentgenograms showed bone destruction). Later: firm nodules in	Died 1 yr. after enucleation and 9 mo. after recurrence was noted	Metastatic retinoblastoma in brain, vertebra, skull and kidneys; bronchopneumonia and pyelonephritis; right eye not remarkable except for

				frontal bone, both temporal bones, left maxilla, molar processes; loss of pain sense below midthigh, weakness in right arm; roentgenograms showed involvement of body of 9th dorsal vertebra, skull and upper ¾ of right humerus; blood in stools; convulsions		metastatic nodule in episclera and external scleral layers at nasal limbus; no tumor foci in retina
19 18 mo.	Left eye: No implant	Evident after 4 mo.; patient given local treatment elsewhere for 3 mo. then referred to Memorial Hospital; 4 to 5 cm. mass in orbit adherent to lids; and surrounding bones; biopsy showed a hematoma within lesion	Mass regressed to ½ original size; residual tissue thought to be organized disintegrated tumor tissue	2 mo. later: hard mass 2.5 cm. near external occipital protuberance and pea-sized mass in left parietal region; 1 mo. later nodule in left mandible, then in left shoulder, lower part of left humerus and lower part of left alveolus	Died 1 yr. 1 mo. after enucleation and 8 mo. after recurrence was noted	Metastasis to skull, 5th right rib, 5th, 6th, 7th left ribs, left humerus, right femur, right tibia, left radius; bilateral deep inguinal and femoral nodes, pancreas; miliary parenchymatous abscesses right lower and upper lobes of lungs
20 2 yr.	Right eye: No implant Left eye: Irradiated elsewhere for 6 mo. (marked regression claimed); to Memorial Hospital after 4 mo., right orbit filled with mass; left eye—retina completely detached and a vascular mass nasally, almost to the posterior lens surface; left eye enucleated; pathologic observations: retinoblastoma, no invasion of optic nerve or emissaria; right eye: orbit exenterated and 5 gold-filtered radium seeds implanted in stump of optic nerve about inferior orbital fissure	Evident after 4 mo. in right orbit	8 days postoperatively, temperature 104 F.; vomiting, ankle jerks hyperactive, hyperesthesia over entire back; considerable purulent discharge from left orbit; patient became comatose, with marked retraction of neck	.....	Died 3 wk. postoperatively; clinical diagnosis: meningitis from implantation of seeds in optic nerve	Acute diffuse fibrinopurulent meningitis and bronchopneumonia; no residual tumor noted
21 4 yr.	Left eye: no implant; pathologic observations: entire vitreous filled with tumor which contained large areas of necrosis; extension through sclera; optic nerve invaded but operative section appeared free	Evident at time of enucleation as a whitish, semicaseous, friable tissue posterior to the globe	Disappearance of tumor in orbit	.....	No evidence of disease 2½ yr. after enucleation and irradiation	

* All these patients received irradiation to the metastatic sites.

TABLE 5.—*Data on 2 Cases of Far Advanced Bilateral Retinoblastoma*

Case, Age, Date First Seen at Memorial Hospital	Clinical Findings	Treatment	Course	Metastases	Outcome	Autopsy
22 3 yr. Oct. 1938 (fig. 1)	Right eye: Vision completely destroyed by growth Left eye: Light perception only Growths so far advanced no treatment advised	None	Oct. 1939: readmitted for terminal care; blind; both eyes protruded; exophthalmos increased; right eye enucleated in December 1939 and left eye in February 1940 for palliative reasons	Nov. 1939: mass in right preauricular region; later in neck, right groin, thoracic cavity and scalp; roentgenogram showed extensive osteolytic lesions of humerus, femurs and bony pelvis and mass in middle of the left side of the chest	Feb. 1940: Died of disease	Direct extension into brain; lymph node metastases (generalized) including cervical, axillary epitrochlear, aortic, iliac, inguinal (all bilateral) and abdominal; every bone involved except hands and feet (mostly subperiosteal); both testicles completely replaced by tumor tissue; no subcutaneous metastases
23 1½ yr. July 1940	Right eye: Retina completely detached, filled with multiple tumor foci; calcium present; tension, 35; left eye: same as in right eye except more advanced; tension, 50	July 1940: bilateral enucleation (specimens preserved intact; no microscopic report)	No evidence of disease	None	Dec. 1940: No evidence of disease; general health good	

would not agree unanimously that death is preferable to blindness. Since the wishes of the one most concerned—the child—cannot be consulted, it seems only fair that life at least should be spared him until he is old enough to decide for himself. If death is considered preferable to blindness in advanced retinoblastoma, then the noninterventionists should logically assume the responsibility for disposing of the patient by euthanasia when the disease reaches the painful terminal stages, in order to prevent the weeks or even months of intense suffering. It is our opinion that any one who has followed even a single case of this form of cancer through its terminal stages will consider it inhumane to withhold immediate enucleation of the eyes, which if it will not effect a cure, at least will have a good chance of obviating much suffering. Sentimentalism in medicine, although well intentioned, too often completely disregards the interests and welfare of the patient.

TABLE 6.—*Classification of Retinoblastoma for Selection of Treatment*

	Method of Treatment
1. Unilateral tumor not extending outside of globe	Enucleation of globe
2. Bilateral tumors	(*a*) Enucleation of the more involved eye and treatment of the other by fractionated radiation if there is a chance of conserving vision
	(*b*) Enucleation of both eyes if the vision is irreparably destroyed
3. Residual * or recurrent tumors after enucleation	Irradiation
4. Widely disseminated retinoblastoma	Palliative treatment by irradiation or surgical excision of individual painful lesions

* Tumor left in nerve or orbit at time of enucleation.

In postoperative recurrent retinoblastoma the prognosis may not be hopeless if the tumor is still limited to the apex of the orbit. When the growth is widely disseminated, palliative irradiation or surgical excision of painful foci of the growth is definitely worth while from the humane standpoint.

On the basis of the foregoing general principles of treatment, retinoblastoma may be classified into four groups as shown in table 6. The rationale of treatment will be discussed first according to the group; there will follow a detailed description of technic under separate headings.

TREATMENT ADVISABLE FOR THE DIFFERENT GROUPS

(1) *Unilateral Retinoblastoma Not Extending Outside the Globe.*—As we have previously mentioned, retinoblastoma is invariably far advanced when first diagnosed, and our attempts to treat unilateral tumors by irradiation have never been successful in eradicating the disease and conserving any vision in the treated eye. In those few instances (cases 1 and 2, figs. 2 and 3) in which we attempted irradi-

ation, the regression of the bulky unilateral tumor after several weeks of treatment was not particularly impressive and we found little to encourage us in the belief that a conservative result (retention of vision with cure of the tumor) could be obtained. If vision could not be conserved by irradiation, we were forced to admit that while we were thus temporizing we undoubtedy were giving the cancerous growth the opportunity to disseminate widely. For these reasons we stopped the irradiation and enucleated the eye. Since 1936 we have not used irradiation in the treatment of unilateral tumors, and at the present time we urge the immediate enucleation of the affected eye.

(2) *Bilateral Retinoblastoma.*—We have already discussed our reasons for advising immediate bilateral enucleation when the growths

Fig. 2 (case 2).—Unilateral retinoblastoma. *A,* on admission, five months after the mother had first noticed the abnormality of the eye, the tumor mass gave a white reflex through the dilated pupil of the right eye. *B,* the white reflex completely disappeared after irradiation. With the ophthalmoscope it seemed that the lesion in the retina was arrested, but there was a large globular elevation which was thought to represent tumor growth in the choroid. The patient died of generalized metastases.

are so far advanced that there is no hope of conserving vision in either eye by irradiation.

When there is a chance of controlling the disease in the less involved eye with conservation of some vision, we advise the immediate enucleation of the more involved eye and radiation therapy to the other. Such radiation therapy is complicated and time consuming and is possible only by the use of special apparatus and by careful attention to many technical details. It is probable that such treatment should be given only in specialized clinics where there is sufficient material for the

accumulation of adequate experience both in administering it and in observing the subsequent course by systematic ophthalmoscopic examinations. When there are sufficient clinical material and average facilities for radiation therapy, it should be possible to develop a satisfactory technic, and we hope that the report of our experience and the description of our technic and apparatus will serve a useful purpose.

As we have previously mentioned,[1] retinoblastoma is a radioresistant neoplasm which cannot be controlled by moderate doses of radiation except in rare instances.[2] Although the eye itself is fairly tolerant to

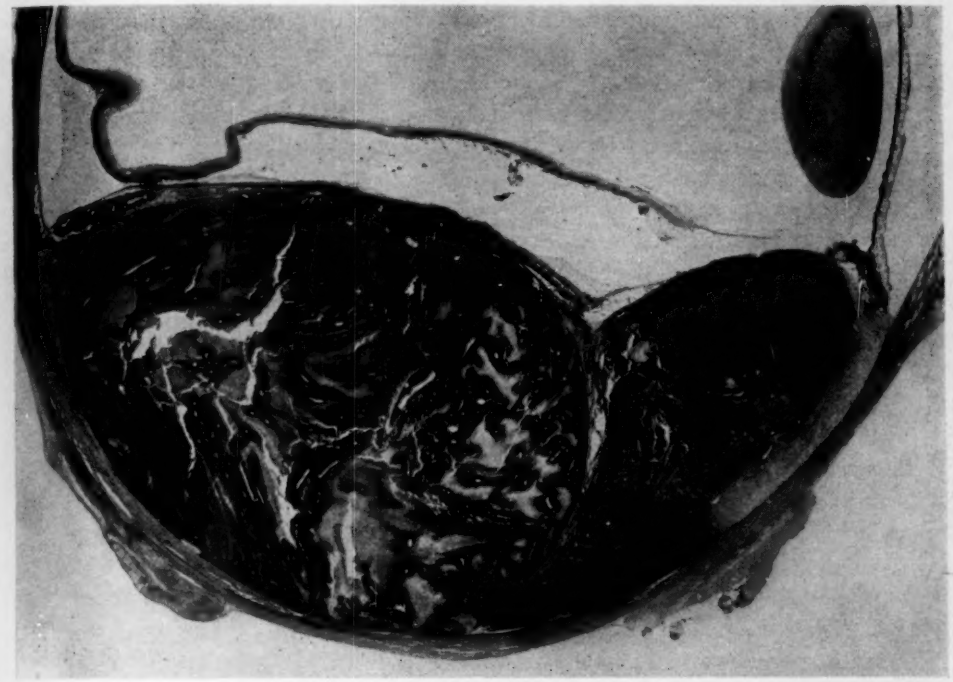

Fig. 3 (case 2).—The tumor is seen growing as a large mass in the uvea; it is divided by a connective tissue septum at about the junction of the ciliary body and the choroid. The overlying retina is somewhat detached and is apparently free of viable tumor tissue.

2. In our previous report [1] we reviewed the literature on the radiation treatment of retinoblastoma and discussed in detail the 3 reported radiation cures, calling attention to the fact that in general the doses were small, about one fiftieth of the dose we have found necessary. The number of reported spontaneous cures of retinoblastoma far exceeds the number of previously recorded radiation cures, and it is entirely possible that the alleged radiation cures by these small doses were merely coincident with spontaneous regression of the tumor. In any event, we are convinced that the attempt to control retinoblastoma by minute doses of radiation is illogical and unjustifiable.

radiation, every possible precaution must be taken to protect the lens and the conjunctiva from the direct beam if the growth is to be destroyed and a useful amount of vision conserved. With special protective measures, fractionated radiation is directed to the posterior portion of the orbit and the growth over a period of four to five months at as high a rate as is possible without production of effects so acute that the treatment must be discontinued. If successful results are to be obtained, the physician and the parents should realize in the beginning that the course of treatment will be tedious, time consuming and onerous; that each daily set-up and each minute of exposure of the child under the x-ray machine require the most scrupulous attention to the smallest details of the technic, and that failure will certainly result from repeated neglect of these details. We know of attempts made after our original publication to treat retinoblastoma by the fractionated irradiation principle without proper attention to the important details; i. e., the child's head was not held in position during treatment, the skin portals were so large as to include the entire globe and the total doses were small. So far as we know, all these attempts were unsuccessful, and we are convinced that unless proper attention is given to details irradiation of retinoblastoma is hardly worth while, since any casual attempt is doomed to failure.

(3) *Residual or Recurrent Retinoblastoma After Enucleation.*—Even though there is an inoperable recurrence in the orbit after enucleation, the prognosis is not necessarily hopeless provided one realizes that retinoblastoma is a radioresistant tumor requiring a heavy dose, which to be tolerated must be confined to the relatively small volume occupied by the tumor. The effect of a cancer lethal dose directed over a large volume of a child's head will be serious and may even be fatal. The refinements in irradiation technic, however, need not be so rigid as when the globe is present and the function of vision is to be conserved. The methods of irradiation used for inoperable recurrent growths are about the same as for other superficial growths, and the technic will be described in a separate section.

After enucleation, the optic nerve should be severed flush with the sclera and prepared immediately as biopsy tissue in order that one may determine whether or not the operative section was beyond any possible invasion of the nerve by the tumor. We believe that if the examination indicates that tumor tissue is present in the portion of the nerve remaining in the orbit, then immediate and adequate irradiation is indicated rather than exenteration. As we shall record in the section on "End Results," the chance of cure in our cases of residual tumor in the optic nerve stump was about three times as good if the irradiation was started immediately after operation instead of deferred until the recurrence was visible and palpable in the orbit.

(4) *Widely Disseminated Retinoblastoma.*—The care of a child with widely disseminated cancer of any variety is a hospital problem, since constant nursing care and the use of facilities not available in the home are required. Too often the patient with incurable cancer receives inadequate attention for the relief of the various complications which arise during the terminal stages of the disease. The common tendency toward the administration of opiates is not alone a solution of this problem. The suffering of the child with widely disseminated retinoblastoma can be markedly alleviated by intelligent nursing care and aggressive surgical treatment or irradiation of the more painful foci of the disease.

TECHNIC OF FRACTIONATED RADIATION TREATMENT FOR RETINOBLASTOMA

The general principles for the treatment of retinoblastoma by fractionated irradiation which we now employ are similar to those described in our previous publication,[1] but as the result of further experience we have made several important modifications in the technic of treatment and in the apparatus. The general principles are: (1) use of two small skin portals (2.5 cm. in diameter), (2) accurate direction of the beam of the roentgen rays and (3) multiple treatments (fifty to sixty) and a high total dose (9,000 to 10,000 roentgens or even more per portal). The modifications in technic which we have introduced since our former report are: (1) use of an improved design of the apparatus which favors more accurate direction of the beam and protection of the cornea, lens and conjunctiva; (2) elimination of the direct beam through the pupil of the eye, and (3) standardization and systematization of the interval and size of the individual and the total doses.

Physical Factors of Roentgen Irradiation.—In order that the greatest possible proportion of the skin dose may reach the tumor, it is essential to employ high voltage roentgen rays (200 to 250 kilovolts) with a filter of 0.5 to 1.5 mm. of copper and long target-skin distances (60 cm. or over). High intensities (milliamperes of current) are indicated so that the time of the treatment may be cut down to the minimum. Except for the size of the skin portals, obtained by the use of special cylinders, as will be discussed in a succeeding section, these physical factors of the irradiation are within the scope of most clinics. The exact physical set-up which we now use is as follows: 250 kilovolts; 30 milliamperes; filter, 1.5 mm. of copper; target-skin distance, 60 cm.; circular portals, 2.5 cm. in diameter, and intensity, about 50 r per minute. The usual single dose of 400 r can, therefore, be given in about eight minutes.

Size, Shape, Number and Location of Skin Portals.—In the intensity necessary for the control of retinoblastoma, all radiation which strikes the uninvolved portions of the eye or the surrounding structures is not

only useless but distinctly harmful, and therefore if one is to deliver an adequate dose to the growth it is essential that the beam of roentgen radiation be confined as far as possible to the immediate area of the tumor. Since the beginning of this work, in 1933, we have used circular portals 2.5 cm. in diameter, which we still believe to be the optimum size. Larger portals cannot be used if the highly injurious effects of direct irradiation of the cornea, lens and conjunctiva are to be avoided.

Since our preliminary report, we have devised two special cylinders, which are shown in detail in figures 4, 5 and 6. By the use of these

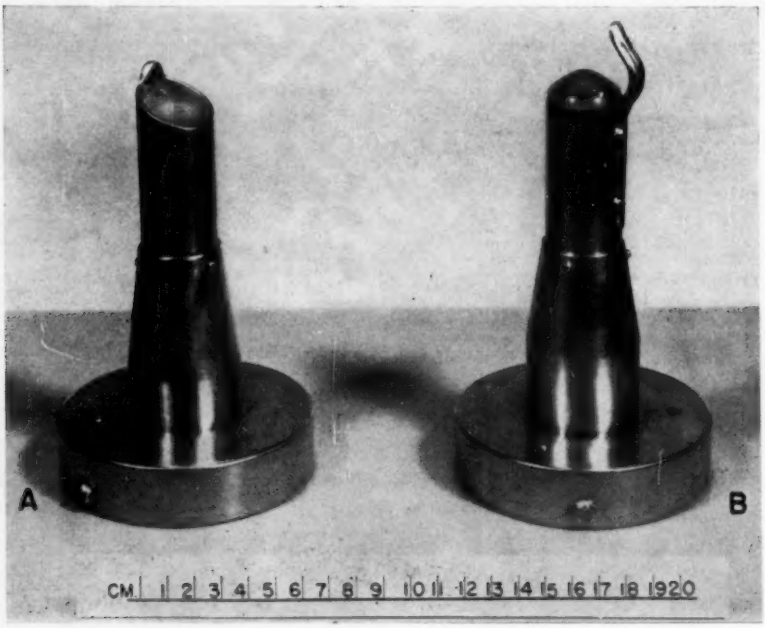

Fig. 4.—Special cylinders for radiation treatment of retinoblastoma. *A* has an oblique distal end to fit against the temple. *B* is applied to the bridge of the nose to irradiate a growth in the retina on the contralateral side. It has a hooked projection to mark the margin of the beam of radiation so that the cornea and the anterior chamber of the eye may be spared. (These devices were constructed in the machine shop of the Memorial Hospital for the Treatment of Cancer and Allied Diseases by Mr. A. Schreiner, master mechanic.)

devices, one may confine the radiation to a beam of small caliber aimed at the posterior wall of the globe, much as one sights along the barrel of a rifle at a small target, avoiding irradiation of the cornea and lens by the direct beam. After further experience we have concluded that the posterior wall of the globe can be irradiated safely only from two cutaneous portals in the positions illustrated in figure 5, rather than from the three portals which we formerly advised. These two portals

are designated as (1) the temporal portal, which is lateral to the outer canthus, and (2) the nasal portal, on the opposite side of the bridge of the nose, the beam being pointed contralaterally and slightly backward.

We originally used a third portal, with the beam pointed directly backward through the pupil of the eye. We are now convinced that this anterior portal should not be employed, because we were never able to administer any great quantity of radiation through it (about 2,500 r) without bringing on troublesome complications—chiefly radiation conjunctivitis and corneal changes. The latter constitute the main deterrents to the administration of a cancer lethal dose of radiation to the posterior wall of the orbit. The omission of this anterior portal always

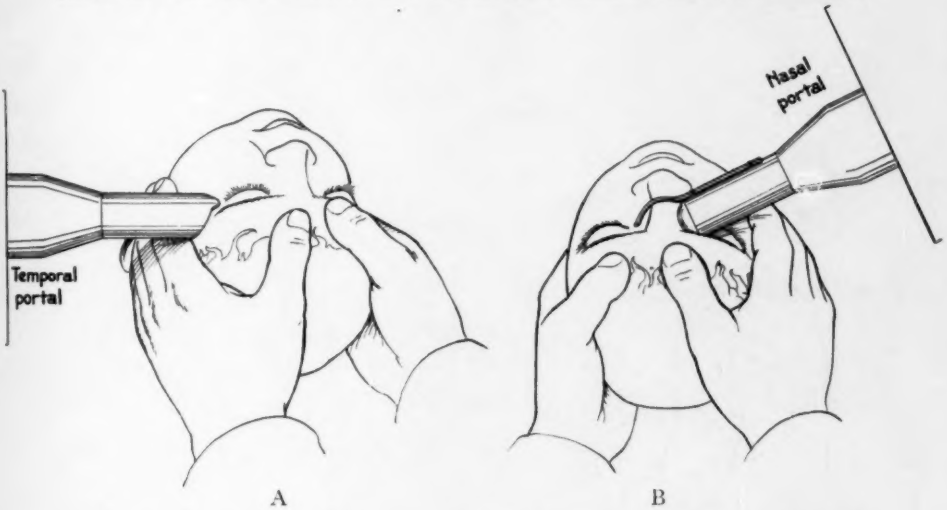

Fig. 5.—Roentgen irradiation of retinoblastoma. *A*, the child's head is being held in position for irradiation of the posterior half of the left globe through a temporal portal. *B*, the child's head is being held in position for irradiation of the posterior wall of the left globe through the opposite side of the bridge of the nose.

reduces the degree of the undesirable effects of radiation in the anterior portion of the globe, although these effects may occur when the other two portals are used if the beams are not accurately centered and directed.

Maintenance of the Globe in Its Correct Relation to the Fixed and Limited Beam of Roentgen Radiation During Treatment.—This is extremely important and a rather difficult task which requires both patience and tact. Even small errors in the direction of the narrow beam are of sufficient significance to determine the difference between success and failure. By the use of special devices, shown in figures 4 and 5, the beam of radiation is aimed at the posterior wall of the globe,

care being taken that it does not strike the anterior wall (cornea and lens). After positioning, the child's head is held in direct and steady contact with the cylinder during treatment.

Up to the age of 5 to 6 years, the child cannot be expected to cooperate, and some one must hold the head firmly in the proper position. This task, we believe, is the duty of the parents or of other members of the family rather than of members of the medical, nursing

Fig. 6.—The child's body is immobilized by being wrapped in a sheet. One of the parents steadies the child's body, and the other holds the head in position during the treatment.

or technical staff. The holding of a crying, struggling baby in a fixed position for ten minutes three times a week over a period of three to four months is onerous, and the slight risk of general exposure of the body from remaining so close to the x-ray tube and of local exposure of the hands while holding the baby's head should be assumed by the family of the child, who have to go through the experience in only 1 case, rather than by members of the staff, who may also have to assume it in other cases. Ordinarily one parent holds the child's head

and the other the body, which is partly stabilized inside a folded bed sheet. The positions and the location of the portals are illustrated diagrammatically in figures 5 and 6.

At the beginning of treatment the parents may naturally be in a highly emotional state, and, even though they have the best of intentions and try to understand the importance of their duties, nevertheless they may find it difficult to carry out instructions. By patiently and repeatedly explaining the importance of this task and the reasons for the parents' undertaking it, and by giving simple descriptions of the local anatomy with regard to the tumor (fig. 7), we have found that we can teach the average parents to do their part acceptably after the first two to three trials.

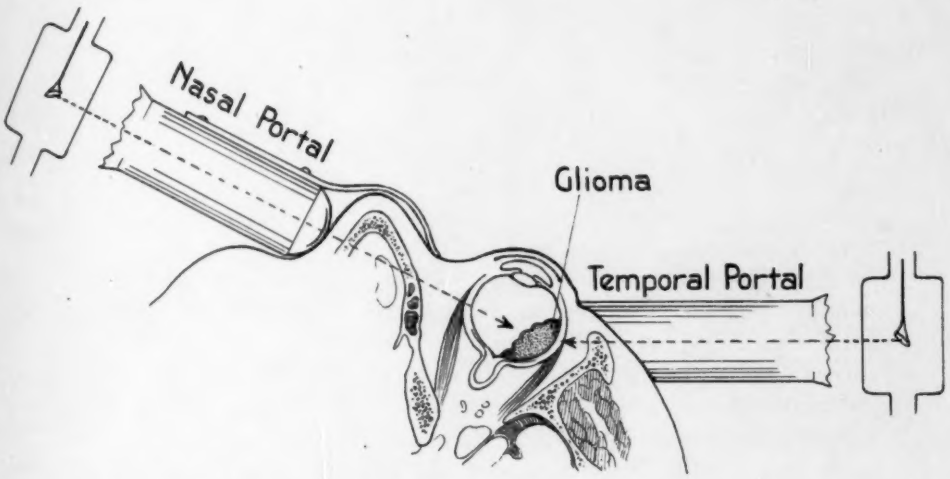

Fig. 7.—Local Anatomy of the Tumor. Cross section diagram showing the path and the objective of the roentgen radiation as directed through each of two portals.

Size of the Individual Dose, Frequency of Treatments, Total Period of Treatment and Total Dose.—These factors must be considered together, since each one depends so much on all the others. With the physical factors already described, we have found that the individual dose should be about 400 r if given three times a week. In deciding on the frequency of treatments, one must compromise to some extent between what would probably be the ideal, that is daily exposure, requiring daily trips to the clinic by both the parents and the child, which might be impractical or even impossible for both financial and physical reasons, and the alternative of giving larger doses at longer intervals. When the home is at some distance from the clinic, it is usually necessary to admit the child to the babies' ward for a period of several months

while treatment is being given. When the home is nearer, the child may remain at home. In the latter case we have found that on the average both the parents and the child can if necessary make three visits a week to the clinic over a period of several months.

When treatment is given three times a week, the two portals (temporal and nasal) are treated alternately so that each is irradiated about every fourth day. Under such a plan the treatments are given regularly without interruption, the aim being the eventual administration of about 8,000 to 10,000 r to each portal, which will require sixteen to eighteen weeks. After the administration of about 2,400 r to a portal, an erythema develops in the skin exposed to the direct beam which in the next four to five weeks may go on to a mild epidermicidal reaction. Such an effect should be welcomed, since it indicates that radiation is being delivered at the optimum rate. After this reaction has developed in the skin, it usually proceeds to heal partially while the treatment is being continued at the same rate as that which produced it, a phenomenon frequently observed in radiation therapy of cancer in general.

Control of the Dose by Observation Externally and Ophthalmoscopically.—As has been mentioned previously, the appearance of radiation erythema going on to a mild epidermicidal reaction at the temporal and nasal portals need not cause alarm. On the other hand, the development of marked conjunctivitis and keratitis with photophobia indicates that there has been an error in the direction of the beam due either to the original set-up or to failure to hold the head steady in its correct relation to the cylinder. If these reactions are not too severe, the treatment may proceed, but with more careful precautions to avoid including the anterior portion of the globe and the conjunctiva in the direct beam. If the misdirection of the beam continues, these effects may become so severe as to necessitate the cessation of treatment. In 3 of our patients, these severe reactions in the anterior portion of the eye caused partial failure, i. e. the loss of vision, even though the growth was permanently controlled (cases 7, 8 and 11).

Ophthalmoscopic examination, with a careful comparison of the appearance of the lesion with that at preceding examinations, should be carried out at two to four week intervals, but despite the ophthalmoscopic appearance the irradiation should be continued to a dose of at least 7,500 r to each portal before termination of the treatment is even considered, since this dose is invariably well tolerated if properly administered. Depending on a lesser dose will too often result in incomplete regression. If there is any doubt about the sterilization of the tumor, the treatment should be carried beyond 8,000 r per portal and continued to at least 10,000 r if necessary. Beyond this point treatment is of doubtful value, since the untoward local effects of radiation are considerable.

CLINICAL COURSE WITH FRACTIONATED RADIATION

During the course of treatment and for one year afterward, each of our patients has a monthly examination of the eye while under general anesthesia; this includes an ophthalmoscopic examination through a dilated pupil and determination of the tension with the tenometer. Notes, diagrams and sketches are made in order that variations in the appearance of the lesion may be compared from time to time. In some cases drawings are made by an artist before treatment is started and after its completion. After treatment is finished and a year has elapsed, each patient is examined every three months.

Cloudiness of the Retina Surrounding the Lesion.—Within the first month after the beginning of treatment, a grayish to yellow-white zone develops in the retina surrounding the lesion, apparently due to edema adjacent to the tumor, a phenomenon which may be observed at any time throughout the course of treatment. This zone is sometimes outlined by a highly refractile reflex ring running concentric to the border of the lesion. In some instances it seems to represent a flat detachment due to the accumulation of a subretinal transudate, particularly in the dependent portion. Such retinal cloudiness must not be confused with a later complication resulting from the extension of the tumor into the choroid, which will be discussed under complications.

Alteration in the Contour of the Lesion.—A change in contour can be followed either by measurement with a grid projected into the ophthalmoscopic field or, less accurately, by estimation in disk diameters. After one to two months there is usually a recession of the borders of the tumor, which often become rarefied, feather edged and irregular in contour. The irregularity often appears first in the upper half, while the lower half seems more sharply demarcated and even overhanging. We have interpreted these phenomena as indicating sufficient dissolution of the tumor tissue to permit it to gravitate somewhat to the more dependent portion, thereby leaving a receded upper border and a sharper, somewhat pendulous lower border. Recession of the border proceeds slowly over a period of from two to six months, as the broken-down tissue is absorbed. The area over which the tumor recedes around the base is identified by a disturbance of the pigmented epithelium which produces either proliferation and resultant changes in the pigment or complete disappearance, resulting in a brighter red reflex from the underlying choroid. Such an appearance indicates recession only at the base of the lesion and not of that part of the tumor which protrudes into the vitreous. Nevertheless, the appearance of this change in the pigmented epithelium, which is seen from the first to the fifth month, is evidence of regression, and as such its accurate location and extent are important.

Decrease in the Height of the Lesion.—We have attempted from time to time to estimate the height of retinal lesions in diopters, a method which did not prove satisfactory, since the margin of possible error was disproportionately large in comparison with the height which we were trying to measure. It is obvious, however, that there is usually a decrease in the height of the lesion commensurate with the recession of its border. As the height decreases, the surface of the tumor usually becomes more irregular in contour.

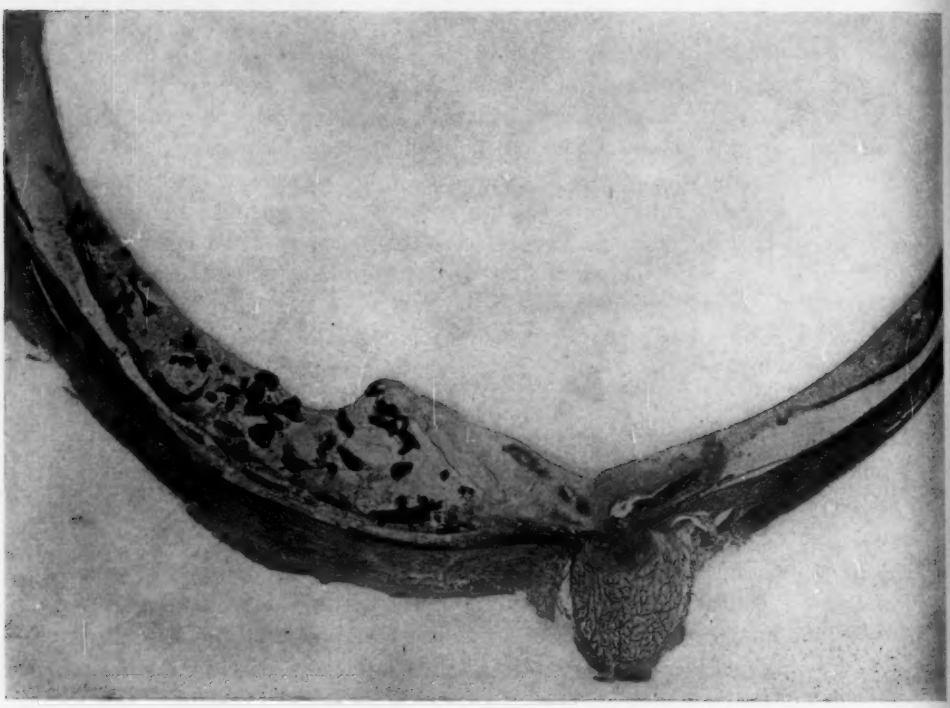

Fig. 8 (case 10).—Right eye. The tumor in the retina has been reduced to foci of solid calcium scattered throughout an area of coagulation necrosis. Viable tumor tissue is present in the underlying choroid.

Vascularity.—After from two to six months the increased vascularity over the surface of the lesion should diminish. The decrease should be progressive, and an increase in the number of vessels in any area is evidence that there is a continuation or resumption of growth. In 2 cases we noted an increase in the vascularity of the lesion at one site just after the originally intended course of irradiation had been completed, and in both we resumed treatment. In 2 other instances, six months and one year, respectively, after treatment was started we noted the appearance of beds of newly formed capillaries together with several

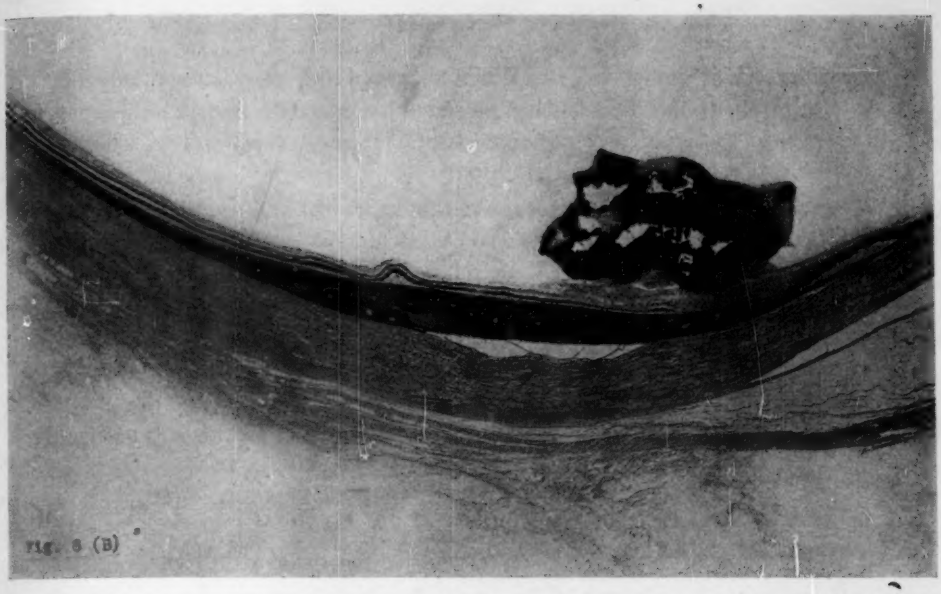

Fig. 9 (case 10).—Left eye. The site of the tumor in the retina has been reduced to a mass of calcium lying in an area of coagulation necrosis. The underlying choroid shows viable tumor tissue with a tendency toward perivascular growth.

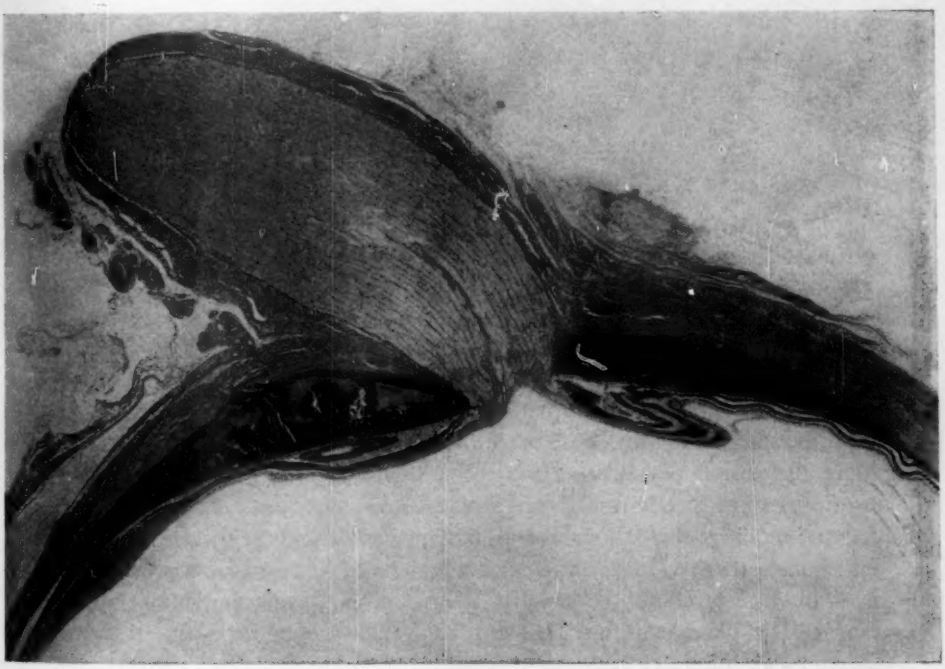

Fig. 10 (case 10).—Left eye. The tumor has extended to the choroid around the optic nerve. The overlying retina shows only one small focus of questionable viable tumor tissue.

small petechial hemorrhages. We interpreted this as representing collateral circulation which had developed after vascular atresia, and since both of the patients have remained free of disease, this finding was not an indication of activity of the tumor.

Calcification.—It is well known that calcification frequently occurs in a nonirradiated retinoblastoma. Calcium is usually seen in the microscopic sections, and Pfeiffer [3] by roentgenograms has demonstrated its presence in 75 per cent of the cases which he has studied. With the ophthalmoscope, small irregular, chalky to pearly white granular areas of calcification can be seen over the surface of the lesion, which, in our opinion, are pathognomonic of retinoblastoma and are never found in the various forms of pseudoretinoblastoma. In the microscopic

Fig. 11.—Diagrammatic sketch of lesions before treatment. The larger lesion extends from the temporal margin of the disk to well beyond the macular region. There is a smaller lesion below the disk.

sections of true retinoblastoma, the calcium is seen in the areas where the tumor tissue has outgrown its blood supply and become necrotic. The treatment of the tumor with roentgen rays according to the method described here tends to cause additional necrosis of the tumor tissue and more deposition of calcium, and ultimately the lesions are reduced for the most part to necrotic tissue and calcium (figs. 8, 9 and 10). The former tends to be absorbed gradually, while the latter persists. The end stage, then, is often a somewhat elevated chalky to pearly white avascular mass composed mostly of calcium and surrounded by some pigmentary changes (figs. 11 and 12). The actual and the relative increase in the calcium content of the lesion as observed ophthalmo-

3. Pfeiffer, R. L.: Roentgenographic Diagnosis of Retinoblastoma, Arch. Ophth. **15**:811-821 (May) 1936.

scopically form one of the best indexes of regression. The increase in the calcium element may be noted from the first to the sixth month. In one of our cases of arrested involvement with good function (case 13, fig. 13)—too recent for the cure to be considered permanent—this calcification has appeared only in a small degree.

Hemorrhages.—Small hemorrhages, which eventually are absorbed, may occur over the surface of the lesion at any time from the first to the tenth month and are sometimes found in proximity to a bed of newly formed capillaries (see "Vascularity"). In our cases no large hemorrhages of consequence have been observed. In a case of advanced retinoblastoma (case 8) in which atrophy of the globe developed, hyphemia was noted.

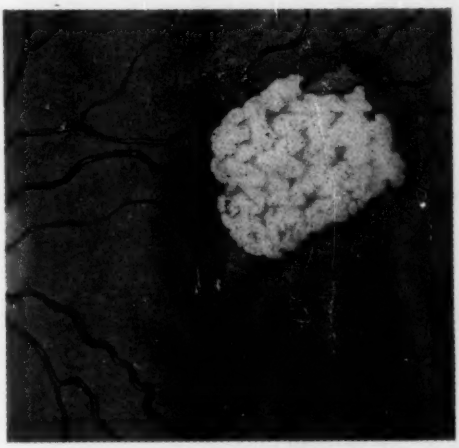

Fig. 12.—Drawing of the larger lesion at the completion of the treatments. There is an elevated chalky white mass with an undulating surface and irregular borders. At the upper and lower borders there is a pigmentary disturbance.

Atrophy of the Iris with Dilatation.—In 2 of the cases in which the growth was arrested (cases 8 and 11) atrophy of the iris developed, following secondary glaucoma after one year and after sixteen months, respectively. The pupils became wide and immobile to light, probably owing to atrophy of the iris.

Posterior Synechias.—In 1 instance, after about fifteen months some posterior synechias developed, probably as the result of mild iritis from dissolution of the tumor tissue by irradiation.

Implantation Growths on the Iris.—In 2 cases, after sixteen and eighteenth months, respectively, in which the tumor was not controlled by irradiation, there appeared on the anterior surface of the iris several small foci of vascularized tumor tissue, representing fragments of the growth which had gained access to the anterior chamber and implanted

themselves on the iris, where they found sufficient blood supply for growth. These were cases of far advanced retinoblastoma obviously out of control, and they terminated fatally.

Extraocular and Adnexal Changes.—The reaction of the skin, conjunctiva and cornea to a given dose of radiation will vary widely in different patients. Some patients will at any time show no more than mild erythema, while in others this reaction may go on to superficial blistering. A variation of lesser degree occurs in the reaction of the conjunctiva and the cornea, but severe changes in these structures are due to errors in direction of the beam more often than to individual hypersensitivity. If an accurately measured dose of 400 r (calculated in air) is given three times a week by the technic which we have described, the absence of marked erythema does not necessarily mean that the dose is ineffective, for some of our best results have been obtained in patients who have shown only mild external reactions. On the other hand, the doses mentioned should produce a slight blistering of the skin in at least 75 per cent of the patients treated. Otherwise there is probably some error in the physical measurements of the output of the x-ray machine. As has been mentioned, a blistering reaction in the skin need cause no alarm. A bland ointment (petrolatum or boric acid ointment) should be applied to the affected area, which usually partially heals during the course of treatment.

During the course of the treatment photophobia and a blush of the eye accompanied by slight changes in the corneal epithelium developed in some of our patients. In these there was a diminution in the luster over the lower one third to one half of the cornea and when the cornea was stained with one of the fluorescent drugs a form of superficial punctate keratitis was noted with the slit lamp. Scrapings of the epithelium stained and examined microscopically showed keratinized superficial epithelial cells. Such keratinized cells desquamate, leaving superficial punctate denuded areas which are made apparent by the stain. Such lesions, frequently seen when the cornea is exposed to a direct beam of radiation, always begin over the lower portion of the cornea, usually remain confined to this area and may be present for long periods with no untoward consequences. The same process seems to take place in the bulbar conjunctiva, particularly over the lower portion.

Beginning about the third month and extending through the fifth, there may be some loss of cilia over the nasal portion of the lower lid and to a lesser extent over the upper lid of the opposite eye. The eyelashes lost may be replaced later by smaller, finer and lighter eyelashes. Following healing of the acute reaction and continuing over a period of several months to a year, there may be atrophy of the subcutaneous tissue of the skin of the bridge of the nose and of the temple which has been exposed to the direct beam of radiation. In the same areas, characteristic postirradiation dryness and telangiectasis may occur later.

Fig. 13 (case 13).—The left eye. *A*, appearance of the tumor before treatment. *B*, appearance of the tumor after three months of treatment. Several small white foci of calcium can be noted over the surface.

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In some instances, there may also be keratinization, or cornification, of the lid margin extending past the gray line to or even beyond the posterior lid margin. These late changes in most of our cases have not been marked enough to constitute an unsightly blemish.

COMPLICATIONS

Extension of the Tumor into the Choroid.—Tumor growth, particularly in advanced stages, sometimes reaches the choroid and in the rich vascular supply grows rapidly, is uncontrolled by irradiation and eventually leads to metastasis. Clinically, the entrance of the growth into the choroid may be noted at first as a diffuse yellowish white elevated area developing at one site along the border of or encircling the previously observed retinal lesion, or it may appear first adjacent to the disk. It continues to grow in extent and elevation until it is a large globular mass protruding into the vitreous, over the surface of which the retinal lesion may be identified.

In the study of pathologic specimens, we have noted that the extension into the choroid may be at a site not only adjacent to the primary lesion but distal to it as a result of implantation growths along the internal choroidal surface. A common pathway of extension from the retina to the choroid is by way of the termination of the lamina vitrea at the optic nerve and along the border tissue into the choroid (fig. 10).

Radiation therapy seems to have little if any effect on the growth when it has invaded the choroid. In both of the fatal cases summarized in table 3 (cases 9 and 10), there was choroidal extension of the growth. It was noted clinically in the first after six months and in the second after nine months of treatment (figs. 8, 9 and 10). A unilateral growth treated by irradiation (case 2, table 2) extended into the choroid and proved fatal (fig. 3).

Glaucoma.—From five to fifteen months after treatment, secondary glaucoma may develop. This complication was encountered in 5 cases (cases 1, 7, 8, 10 and 11). The underlying changes which cause it are no clearer than those which occasionally produce secondary glaucoma in any eye which has been in the pathway of radiation. It is more often intractable than any other type of glaucoma; in our cases repeated trephine operations and in 1 instance (case 11) an iridotasis operation were of no avail, and the eyes all became atrophic. In none of our cases did glaucoma develop when the treated lesion was small.

Cataract.—In 5 cases (cases 5, 6, 7, 8 and 11), a cataract was noted. In 2 of the 5 cases, in which the retinoblastoma appeared to be arrested and the eye well functioning, there was a pure radiation cataract. In one it appeared five years after treatment, was only a small dot in the posterior part of the cortex away from the pupillary area and did not in

any way interfere with vision (case 5, fig. 14). In the other it appeared three and a half years after treatment, progressed to maturity and required a linear extraction. In the other 3 of these 5 cases no changes have appeared in the lens at the time of writing. In the other 3 cases in which a cataract developed it appeared after secondary glaucoma when the eye was proceeding toward atrophy. The cataracts in these cases cannot be classed as pure radiation cataracts, as it is not clear to what extent they may have been due to the serious complications of the disease.

Fig. 14 (case 5).—The patient January 1941. She had bilateral retinoblastoma. The more involved eye (right) was enucleated, and the remaining eye (left) was treated by irradiation. At the time of writing she was 9 years old, with no evidence of disease eight years after treatment. She wears a prosthesis on the right and has vision of 20/25 in the left eye. She has made normal progress in school and is now in the fourth grade.

Pannus Formation.—In 3 cases (cases 7, 8 and 11), in which the growth was arrested permanently but the eye became atrophic, a superficial vascular membrane developed on the cornea after four to fifteen months. This complication began primarily at the limbus below and was noted first over the lower portion of the cornea, with later involvement of the entire structure, producing an unevenness of the corneal surface, a lack of luster and a diminution of transparency.

Detachment of the Retina.—In an eye with multiple large retinoblastomas treated by a few massive doses of radiation at the Memorial Hospital for the Treatment of Cancer and Allied Diseases some years ago and not included in the present series, a detachment of the retina developed after the disappearance of the tumor. Microscopic examination showed that this was due to the shortening of the retina through contracture of the scar tissue in it. The detachment viewed ophthalmoscopically gave a false appearance of progression of the tumor. So far, in the groups of cases reported here we have had no detachment of the retina. The chorioretinal adhesion over the site of the lesion tends to prevent detachment. As previously mentioned, an extension of the tumor into the choroid can be confused with a retinal detachment.

Atrophy of the Globe.—Three of the globes treated (cases 7, 8 and 11) became atrophic after two years and eventually became phthisical. In each the involvement was rather advanced, with multiple lesions in the retina, and it was obvious from the beginning that the eye did not tolerate radiation well, as evidenced by the severe cutaneous and conjunctival reaction, the development of dense pannus over the cornea and the appearance of secondary glaucoma. The conjunctiva showed large telangiectatic vessels, and the cornea finally became completely opaque, vascularized and shrunken. All of the conjunctiva and the corneal epithelium became keratinized and thus xerotic. The tendency to keratinization may be marked and may lead to the formation of large elevated masses of keratin on the cornea, which eventually desquamates en masse, only to reform later. Finally, there may be some entropion of the lid margins, symblepharon and marked contraction of the palpebral aperture.

Summary of Complications Following Radiation.—In general, irradiation of the eye tends to keratinize the conjunctiva and the corneal epithelium, the extent of keratinization varying with the individual patient. Many of the complications mentioned represent only degrees of this process. The sequence of the various stages is approximately as follows: superficial punctate keratitis, pannus formation, extension of the keratinized half of the lid margin over the gray line toward the conjunctiva, xerosis of the conjunctiva and the cornea and, finally, entropion of the lid margins, symblepharon and contraction of the palpebral aperture. The complications can in the main be reduced to four more or less independent conditions: (1) keratinization of the conjunctiva and of the corneal epithelium and its sequelae, as described; (2) glaucoma; (3) cataract; and (4) choroidal extension. Whether or not keratinization and its sequelae assume serious proportions depends in some measure on the individual tolerance to radiation, a factor over which the physician has no control. Whether or not glaucoma develops

seems to depend to a great extent on the size of the lesion treated, and it may be secondary to uveitis from dissolution of tumor tissue. We have never encountered glaucoma as a complication following the treatment of a small lesion. Whether or not cataract develops depends to some extent on individual susceptibility. In treating all types of lesions around the eye we have been impressed with the inconsistency between the dose given and the subsequent changes in the lens. In any event, the most effective means of preventing serious ocular complications is to make certain that the direct beam of radiation does not strike the lens, the cornea or the conjunctiva.

TREATMENT OF RESIDUAL OR RECURRENT RETINOBLASTOMA IN THE ORBIT AFTER ENUCLEATION

The problem of radiation therapy of local postoperative recurrences of retinoblastoma in the orbit or of residual tumors left after operation does not differ materially from that of other superficial growths. Since the eye has been removed, the elaborate precautions already described, the purpose of which is to conserve function in the treated eye, are not applicable, so that fractionated radiation should be given in heavy daily doses over a period of three to four weeks rather than of several months, and this treatment on completion may be supplemented immediately by the interstitial application of radon. The roentgen radiation is given through cylinders slightly larger (3 to 3.5 cm.) than those shown in figure 4 and at shorter target-skin distances (35 to 50 cm.) and is directed anteroposteriorly. Over a period of three to four weeks 7,000 to 9,000 r may be given and immediately on the completion of this dose supplementary radon seeds (5 to 10 millicuries) inserted. Such treatment brings on acute radiation effects in the skin and the conjunctiva, which in the absence of the eye itself are not particularly painful or distressing. If the growth recurs several months after this dose (or even half of it), the treatment cannot be repeated without producing radionecrosis, and therefore it is important to give the higher dose in the beginning in an attempt to sterilize the tumor in the orbit completely rather than to risk the recurrence of partially devitalized cancer a few months after a lesser dose. When such residual or recurrent cancer exists in an irradiated field, its radioresistance and that of the normal tissues will be about equal, so that the differential effect (greater radiosensitivity of cancer as compared with normal tissue) is no longer present and radiation therapy is useless.

TREATMENT OF WIDELY DISSEMINATED RETINOBLASTOMA

The possible variations in the palliative treatment of individual patients with wide dissemination of retinoblastoma do not differ mate-

rially from those in the treatment of any form of widely disseminated cancer. The principles and technic involved are too broad to come within the scope of this report.

END RESULTS

It is well known that retinoblastoma is unilateral in about 75 per cent of all cases, and in these enucleation is usually performed through the eye clinic where the patient is first seen, with permanent cure in 50 per cent. The patients are seldom referred to a cancer clinic and in our series comprised less than 10 per cent of the total. Our series

TABLE 7.—*End Results in the Treatment of Bilateral Retinoblastoma at the Memorial Hospital for the Treatment of Cancer and Allied Diseases 1930 to 1940 Inclusive by Enucleation of One Eye and Fractionated Irradiation of the Other*

Total number of patients		10	
Alive and well		8	(80%)
With vision	5	(50%)	
Without vision	3		
Dead of disease		2	

TABLE 8.—*End Results in the Treatment of Residual and Recurrent Retinoblastoma at the Memorial Hospital for the Treatment of Cancer and Allied Diseases 1930 to 1940 Inclusive*

Total number of patients		7
Patients with residual retinoblastoma		
Living and well	2	
Dead	1	
Patients with recurrent retinoblastoma		
Living and well	1	
Dead	3	

consists mainly of patients with bilateral growths and patients in whom the disease was far advanced, recurrent or residual in the nerve or orbit after operation. The percentage rate of cure for the entire series would therefore have little significance, since it is not truly representative for retinoblastoma in general. For this reason we shall give the end results by percentage only for groups 2 and 3. The former is made up of patients with bilateral tumors in whom the vision had not been completely destroyed in the less involved eye and whose treatment consisted of enucleation of one eye and fractionated radiation to the other (table 7), and the latter is made up of patients with residual or recurrent retinoblastoma (table 8). Of the 10 patients in group 2, 8 are alive at the time of writing, with apparent control of the disease. Of these, 5 have satisfactory vision after seven years, six years, two and a quarter years, two years, and 3 months, respectively. In the fifth case, the treatment

has only recently been completed, but the growth is apparently satisfactorily controlled. The other 3 of the 8 patients are alive, with control of the disease but with no vision in the treated eye. Two died of the disease. Of the 7 patients in group 3, 1 of the 4 with recurrent tumor in the orbit is living and well while 3 are dead. Of the 3 patients with residual tumor in the orbit, 2 are living and well, and 1 is dead. If group 3 for 1916 to 1929 inclusive (table 1) is combined with group 3 for 1930 to 1940 inclusive (table 8), it will be seen that there is a total of 6 patients with residual tumor left in the nerve at the time of enucleation, with 2 dead of the disease and 4 apparently living and well. There are 9 patients with recurrent tumor in the orbit after enucleation, all of whom are dead except 1. These figures would indicate that if it is known immediately after enucleation that tumor has been left in the optic nerve, the patient has over a 66 per cent chance of recovery with immediate irradiation, and that if such residual tumor is not known to be present, and is detected only when it appears as a recurrence, then there is only about a 10 per cent chance of recovery.

SUMMARY

A detailed report is made on 23 patients with retinoblastoma who were referred to the Memorial Hospital for the Treatment of Cancer and Allied Diseases during the years 1930 to 1940 inclusive. This series does not represent retinoblastoma in general, since the majority of the patients were referred because of advanced or bilateral tumors. The selection of the method of treatment for retinoblastoma is discussed, and the technics of the various types of treatment are described. The main purpose of this report is to discuss a method of treatment for bilateral retinoblastoma which consists of enucleation of the more involved eye and radiation therapy to the other in an attempt to control the disease and conserve vision. The technic of the radiation therapy is described in detail. The series of 10 patients with bilateral retinoblastoma includes 8 in whom treatment was successful, vision being satisfactory in 5 after seven years, six years, two and a quarter years, two years, and three months, respectively. Pathologic observations are reported in detail only for eyes enucleated after receiving radiation.

STUDIES OF THE RETINA IN BULK

SOME OBSERVATIONS ON THE UNSTAINED HUMAN RETINA

PROF. DR. ARNOLD LOEWENSTEIN
GLASGOW, SCOTLAND

GENERAL CONSIDERATIONS

The study of the finer retinal details is a work filling the whole life of scientists. Some of these, such as Ramón y Cajal, Held, Max Schultze, Río Hortega, Schaffer and Mawas, used the most delicate methods of hardening, embedding and staining and published an admirable record of most important results. Other investigators, e. g. Fortin, remained independent in their opinion—sometimes different from the acknowledged one.

I want to describe here, with the help of some photomicrographs, a method not generally used by the histologist and its results. My teachers of histology, the well known Siegmund Mayer and Alfred Kohn, stressed the fact that by observing the unstained tissue one would learn many new details and realize the true nature of the organic structure sometimes better than by fixing, embedding and staining. The more complicated the methods the more decomposition of the texture one has to expect and the greater is the danger of getting artefacts.

As an assistant in the department of anatomy in Prague under Carl Rabl and Rudolf Fick, I used a mixture of potassium hydroxide and glycerin to clear embryos for macroscopic studies and to show the development of the nuclei of the bones. Following up a recent series of experiments on lipoid feeding of rabbits, I tried to use this method on ocular tissues, and especially on the retina. As the results seemed to be better than I had hoped, I used this method too on the human retina.

As excision of a whole eye from a corpse is not allowed, the eye is injected as soon as possible after death with a solution of formaldehyde (1 : 10 dilution of the standard 40 per cent solution). At the autopsy the roof of the orbit is removed, the bulb and the optic nerve are laid free from above and the posterior half of the eye

From the Tennent Memorial Institute, Glasgow University (Prof. A. J. Ballantyne).

with the optic nerve is excised and put in the solution of formaldehyde. Fixing for twenty-four hours is enough. The formaldehyde is washed out for five hours, and the vitreous attached to the retina is completely removed. This has to be done very carefully. Then the retina is detached by a gentle stream of water from all sides, until it is free up to the optic nerve. A sharp knife cuts the nerve, and the retina is washed once more and put into a solution of 10 per cent potassium hydroxide and glycerin (50 per cent of each) for six to eight hours. Then it is washed again with water and mounted in warm glycerin jelly or in glycerin and sealed with a good border of turpentine lack or Canada balsam. Air bubbles are best expelled by placing lead-filled cartridges on the slides. The slides are ready and remain unchanged for months (perhaps for years).

Histologists may be able to modify the technic and to obtain even better results. Studies of the stained retina in bulk have been recommended by Shaw-Dunn,[1] Magitot, Jonas Friedenwald, Kyrieleis and others, especially for albuminuric retinitis.

While the retina is opaque in a solution of formaldehyde or water, it thus clears up just enough to be seen with the highest power microscopic magnification, the narrow iris diaphragm of the condenser being used.

The color of the macular area is an intense yellow-green, which remains unchanged for months—a convincing demonstration for teaching purposes. The color resembles or is identical with the yellow of the central area seen ophthalmoscopically with a quartz mercury vapor lamp. The wall of the macula is a deeper yellow than the clearer fovea. In handling this delicate part the greatest care is required, as the macular area is easily torn. The larger the piece of retina used, the more difficult is the preparation. An area up to 1 sq. cm. is the most convenient size for the study of details.

While controlling the slide in water under the microscope I have twice seen (in eyes excised for twenty-four to forty-eight hours) a regular movement of the content of some larger vessels, like that often demonstrated within the mesenterium of a frog. It may be an osmotic process, due to the invasion of water through the vessel walls. It is an amusing phenomenon. The movement of the blood in these vessels stopped after a quarter of an hour.

The vessels are clearly seen. They are normally reddish brown when they contain blood corpuscles. The smaller vessels can be followed as far as the capillary system with its even caliber (Fortin), where

1. Shaw-Dunn: Personal communication to the author.

one blood corpuscle fills the whole lumen and is very often deformed by the pressure of the wall of the vessel.

The capillary system is especially well observed in the macular area, but no loops are recognizable in my slides, only singular capillaries. As the loops are seen very well entoptically by different methods (Gescher, Fortin [2] and Scherer) and even reproduced by injection (Colin Campbell), their absence in my slides is probably due to the different technic. I have no reason to doubt the existence of these loops.

The vessel-free zone is studied without difficulty in certain cases. It is practically circular, and I found it measured about 0.165 mm. in diameter. This zone was found by Gescher to be 0.482 mm. in diameter, by Abelsdorff and Nagel 0.41 mm., by Adler (1929) 0.4 to 0.5 mm. and by Salzmann 0.4 to 0.5 mm. Eisler [3] (1930) stressed the individual differences and favored the record of 0.3 to 0.8 mm.

I used to place the retina with the nerve fiber layer upward so that this layer could be recognized easily. It is clearly seen how the nerve fibers are lifted up by the larger vessels and thus change their direction. The different bundles of the nerve fibers are to be seen, though sometimes with a narrow diaphragm only. Tiny bridging fibers—perhaps glial bundles—are seen refracting light intensely. They lie like cobwebs around the bundles of the nerve fibers. They are to be seen best near the disk. It is not impossible that they correspond to the inserting feet of the glial Müller fibers at the internal limiting membrane. In a case of papilledema the regular nerve fiber bundles were separated one from the other by a more granulated strip with luminous light-refracting spider web–shaped strings. The connection between the surface vessel system and the light-refracting retinal scaffold can be realized in kittens' retinas (cleared with potassium hydroxide and glycerin and unstained in bulk). Not rarely the internal limiting membrane is injured by handling larger pieces of the retina. There the nerve fibers stand up very irregularly, forming a brushlike surface. Here the scaffolding function of this membrane is clearly recognizable.

The medium layers of the retina do not appear so distinct or of such clear architecture with the technic described as the higher and deeper ones. In the latter there is a marvelous picture of the rods and cones in relief, of sharkskin pattern, especially with the stereoscopic microscope. It is easy to count the ratio of rods and cones there (fig. 1 *A*) (all photomicrographs are reproduced without retouching), that is, about

2. Fortin, E. P.: Semana méd. **32** (pt. 2):126, 1925.

3. Eisler, P., in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1930, vol. 1, p. 156.

10 to 15 microns higher than the basic end of the retina, measured with the vernier of the microscope. When I studied the unstained retina in bulk in the reverse order, I verified that the shape of the rods and cones design is unchanged.

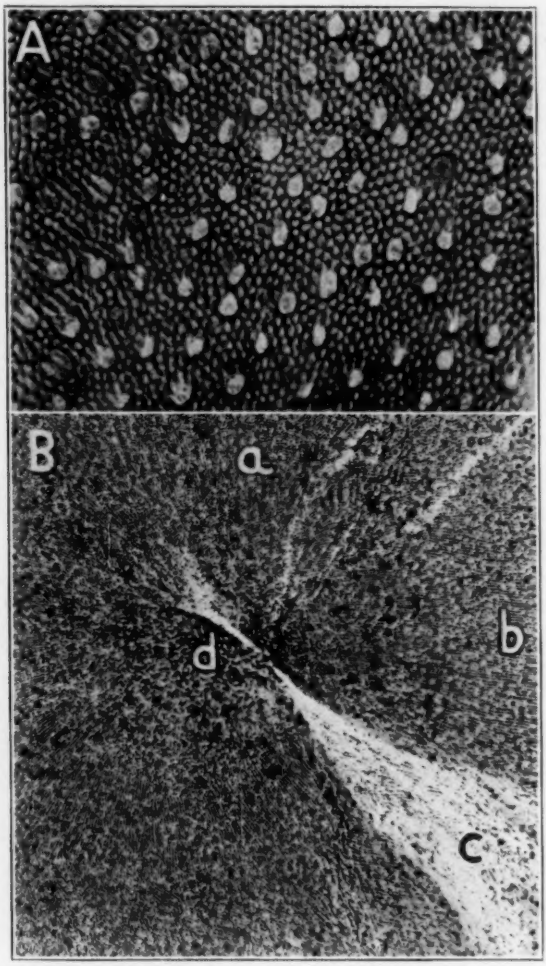

Fig. 1.—*A*, normal retina in bulk (unstained), showing rods and cones some millimeters from the macular area and 10 microns higher than the finger print pattern. *B*, foveal finger print design, showing (*a*) regular crisscross, (*b*) parallel system of lines, (*c*) artificial rupture and (*d*) central pigment needles at the posterior retinal surface.

The distribution of the rods and cones is, of course, very different within the various parts of the retina. I believe that the shagreen leather appearance is produced by the important border between outer

and inner limbs of the bacillary layer. There must be a great difference in the refractive index in this zone. I saw a bright light-refracting borderline system around the rods and cones, which I assumed to be cement framing. I was not successful in bringing out this picture with the photomicrographs.

A most amazing and hitherto undescribed image is to be seen when one focuses 10 to 12 microns deeper and realizes because of the presence of pigment needles that the posterior side of the retina in bulk is being observed. It is different within the macular area and at some distance from the latter. At the macula, especially in the foveal area, one recog-

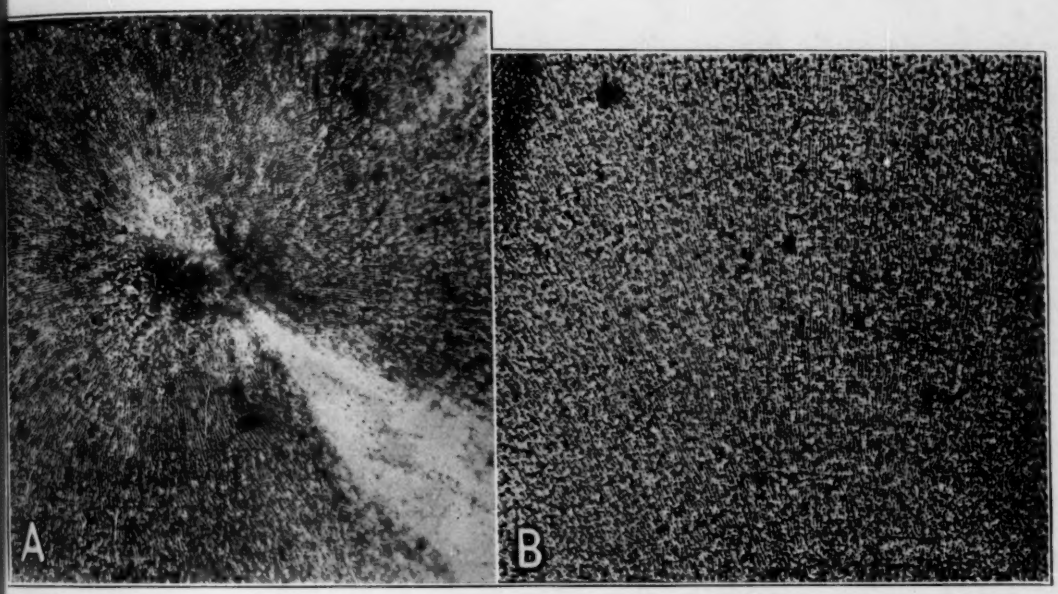

Fig. 2.—Photomicrographs (high power) showing (*A*) macular crisscross of finger print design, different level of the fovea and clivus maculae and (*B*) parallel pattern some millimeters from the macular area. The dark spots are unfocused groups of pigmented needles. The darker portion in the upper left hand corner is the shadow of a larger vessel.

nizes a crisscross of fine, regular lines—a honey-comb-like structure (figs. 1 *B* and 2 *A*). When I first saw it, I believed that I was observing a purely optical phenomenon without anatomic foundation. It is best seen by focusing on the fine, pigmented needles at the posterior retinal surface and then raising the focus 5 to 7 microns with the vernier.

The density of the linear system is not very different, though a little broader in the periphery. I measured 2 microns in the foveal area and a little more than 3 microns nearer the periphery. The crisscross

of the macular area is not always right angled; in some places the angles are acute. The parallelism of the lines is not strictly kept, but with the highest dry power magnification or with the oil immersion objective, one can see some wavelike connecting lines. They show a certain convergence to some point, most marked in the macular area. As the level of the foveal base is not identical with that of the dorsum foveae, both the base and the dorsum are not seen clearly in the same photograph. This image reminds me of a finger print, and so I call these lines the finger print lines of the retina (fig. 2 *B*). At some places I noticed that the lines which were parallel in one layer were crossed by other lines 5 to 7 microns deeper. Thus, the pattern is not a simple one.

As soon as I realized that this system was real, I tried to determine the nature of the observations. I used the polarizing microscope and found no double refraction. Then I studied different kinds of retinal tissue, cross and flat sections, stained and unstained. Sometimes in thicker celloidin (pyroxylin) sections, especially in overstained ones, the direction of the slim rods in the outer limbs (fig. 3 *A*) is not always the same. I should compare it to a waving corn field. At some spots a crisscross (fig. 3 *A*) of these outer limbs occurs. I did not succeed all the time in obtaining truly flat sections of the retina—they were often oblique. Here I could prove that the slim rods lay parallel like hairs, while their peripheral part built up a regular crisscross. In frozen sections stained with gold chloride (Ramón y Cajal) it can be seen that the outer limbs arrange themselves in parallel lines and that to each base cell belong 5 to 6 purple-stained hairlines (fig. 3 *B* and 4 *A*). I cannot explain the remarkable phenomenon that the peripheral part of the bacillary layer is stained with glial stain while the basic cells are not stained with this substance.

The linear and crisscross system pictured here seems to be fibrils of the outer limbs of the rods or scaffolding between these fibrils of the outer limbs. I was able to stain these with glial stain. They seem to produce such a parallel system of lines by coming together end to end. The denser system of the rodlike cones in the macular area, where the slim outer limbs meet converging from all sides, produces the crisscross pattern. The thinner the fibers the narrower the lines and the crisscross of the design. The thinnest pattern is located within the macular area.

The pressure of the cover glass gives the crisscrossed lines the appearance of a membrane, an impression which is very strong. I cannot prove that this linear system is the canal system for the nourishment of the neuroepithelium, but it seems to me not unlikely. The lymph stream which leaves the choriocapillaris passes the filter of Bruch's membrane with the pigment epithelium and enters the retina here in this glial canal system. It is interesting to follow the pigment

corpuscles of the pigment epithelium, which are round at the base of the epithelial cells and needle shaped in the higher, inner parts of the cell (Raehlmann [4]). The needles are all arranged vertically to the base of the pigment epithelium, parallel to the axis of the neuroepithelial cells. Although I have examined this arrangement with special care I have not seen pigmented needles between the neuroepithelial cells.

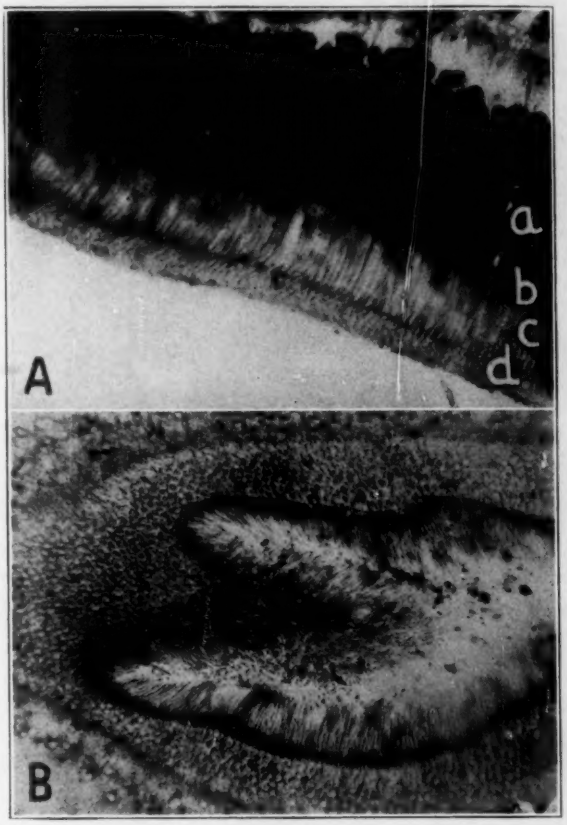

Fig. 3.—*A*, normal retina (embedded in celloidin and stained with hematoxylin and eosin), showing (*a*) outer nuclear layer, (*b*) membrana limitans externa, (*c*) rods and (*d*) crisscross of the outer limbs of the rods and cones. *B*, flat section of the human retina stained with gold chloride (Ramón y Cajal), embedded in gelatin, showing long and cross sections of the neuroepithelial fibers.

I did not find any reference in the literature even hinting at the existence of the system described. Verhoeff [5] described a hitherto

4. Raehlmann, E.: Ztschr. f. Augenh. **17**:1, 1907.

5. Verhoeff, F. H.: A Hitherto Undescribed Membrane of the Eye and Its Significance, Boston M. & S. J. **149**:456-458, 1903.

unknown membrane of the eye. The membrana limitans externa continues at the margin of the disk and passes into the layer of the pigment epithelium, where it can be followed until the pigmentation, gradually increasing in density, hides it from view. In sections bleached by the method of Alfieri, it was proved that this membrane was present in the pigment layer throughout the fundus. Mallory's phosphotungstic acid stain is the best stain for this membrane. The appearance of this mem-

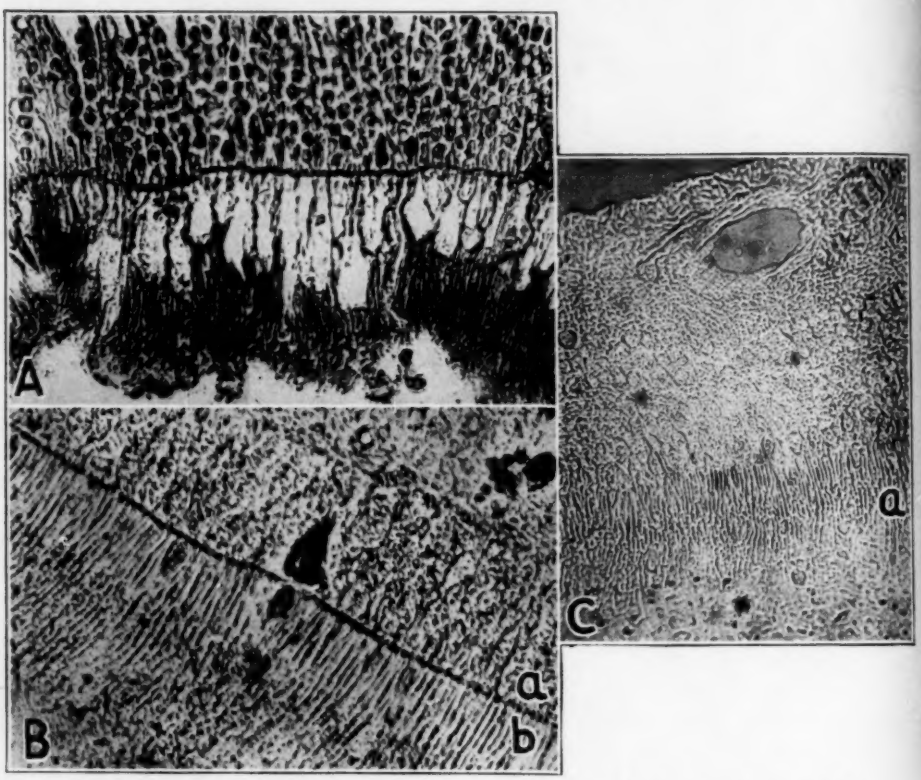

Fig. 4.—*A*, frozen cross section (stained with gold chloride [Ramón y Cajal]), showing membrana limitans externa, rods and cones. The outer limbs are purple and the inner limbs unstained. *B*, frozen cross section (stained with scarlet red, without nuclear staining), showing (*a*) fatty focus within the outer nuclear layer and (*b*) corresponding degeneration of one cone. *C*, unstained cross section of the retina (embedded in gelatin), showing neuroepithelial fibers (*a*) which can be followed up into the outer nuclear layer.

brane in cross sections is that of a delicate line near the inner margin of the cells. It seems to be a true fenestrated membrane. It stains blue with Mallory's stain. This membrane is similar to the membrana limitans externa, giving the stain reaction of neuroglia. Verhoeff

stressed the amazing and interesting idea that rods and cones are not nervous elements but modified ependymal cells. I have not the impression that Verhoeff's membrane is identical with the finger print design, which has apparently the pattern of the fibrils of the outer layer of the neuroepithelium. A relationship cannot be ruled out.

It is easy to observe the nuclei of the bacillary layer in unstained sections. I was able to stain such frozen sections from a case of retinitis albuminurica with scarlet red and found the metabolic unity between the nuclei on both sides of the membrane (fig. 4 *B*). A deep scarlet red spot at the inner part (outer nuclear layer) corresponds exactly to the granular degeneration of one of the cones.

In unstained cross sections one is able to follow highly refracting fibers reaching from the outer end of the neuroepithelium between the single rods and cones. These pass the membrana limitans externa, appearing as a real lamina cribrosa, and are lost within the outer nuclear layer (fig. 4 *C*). My impression is that this appearance, noticeable in all unstained cross sections, is produced by the glial fibers within the neuroepithelium. These fibers are important as a scaffolding of the retinal tissue. Its relation to the finger print design seems probable.

SUMMARY OF PART I

The examination of the unstained human retina in bulk cleared with potassium hydroxide and glycerin and viewed with the binocular microscope with narrow iris diaphragm shows many remarkable facts: The nerve fiber bundles appear raised by blood-containing vessels. The bundles are bound together by fine, light-refracting (glial) cross fibers. The border planes between inner and outer limbs of the bacillary layer show a clear distribution of rods and cones. The yellow macular area keeps its color in slides so prepared for months, and its capillary system is clearly visible. The vessel-free circular area measures 0.165 mm. A finger print design appears at the border between retina and pigment epithelium and is probably of importance for the architecture as a scaffolding and for the nourishment of the neuroepithelial layer. It is thought to be the glial fibers of the outer limbs of the bacillary layer or the glial scaffolding between the neuroepithelial elements.

RETINAL VESSEL SYSTEM EXAMINED IN BULK

Professor Shaw-Dunn[6] has recommended staining the retina in bulk with a stain for fat and studying the spread of lipoid substances within the tissue in cases of retinitis albuminurica. He used sudan IV

6. According to a personal communication, Professor Shaw-Dunn has used this method since 1916.

for this purpose. In his slides, which I was privileged to study, the retinal lipoid spots are stained intensely red (fig. 5 *A*), while some of the larger vessels contain red-stained masses in their wall. Details, of course, were not recognizable. However, the method gives a good survey of the rough distribution of lipoid in the retina and was used by Magitot, Kyrieleis and Jonas Friedenwald in combination with other fat stains (osmic acid).

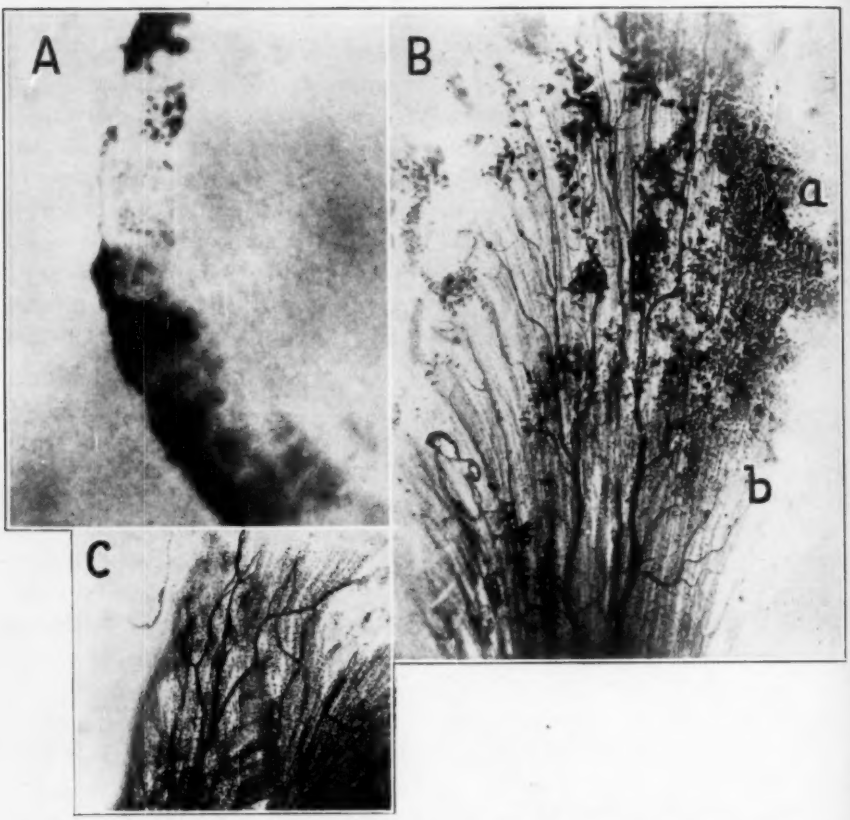

Fig. 5.—*A*, retina (stained with scarlet red), showing fatty infiltration of the wall of a large artery. *B*, retina of a cholesterol-fed rabbit (stained with scarlet red; low power), showing (*a*) the red spots scattered over the whole surface of the retina and (*b*) the reddish brown medullated fibers. *C*, retina of rabbit (stained with scarlet red) fed cholesterol for five months, showing hairpin-shaped end loops (low power).

During an experimental study of the lipoid changes in rabbits fed cholesterol for a considerable time—the results of which will be published in another paper—I examined a retina cleared with potassium

hydroxide and glycerin. The retina was stained with scarlet red, which gives a better result than sudan III or osmic acid. The technic of this staining is a bit more delicate than usual and is as follows:

Alcohol (dehydrated)	40 parts
Sodium hydroxide solution (10 per cent)	20 parts
Distilled water	10 parts
Scarlet red, to excess.	

Dissolve for one hour in an incubator. Filter through three layers of filter paper and stain at about 20 C. Wash the section, float carefully onto a slide and mount in glycerin jelly.

Spielmeyer [7] complained that the method did not give as good results as he had obtained before 1914 and that precipitates disturbed the clear view. I can confirm this. The precipitates are all at the surface of the retina and are of equal size. One soon learns to differentiate these artefacts from lipoid corpuscles by their size and color.

If the retina of rabbits fed for two to six months with 0.5 to 1 Gm. of cholesterol in an olive oil solution daily added to the normal feeding is treated as described, using the method of clearing the retina in bulk with potassium hydroxide and glycerin, the whole retinal vessel system becomes clearly marked in bright red (fig. 5 *B* and *C*). It is the rarely interrupted content of the vessels which stains red when a certain amount of lipoid is reached. The brownish red medullated nerve fibers are thinner the farther they are from the disk. Scattered red shining deep-lying spots within the retinal tissue are lipoid changes of the deeper retinal layers.

The vessel tree is limited to the extension of the medullated fiber zone. The retina of the rabbit is—as is well known—a merangiotic one. The end loops of the arteries are clearly outlined. They bend very sharply, sometimes with hairpin bends, reminding one of the capillaries of the vessels described by Wislocki and Campbell [8] in the brain of the opossum. The breadth of these end loops is greater than that of the human retinal capillaries. The end loops measured 7.5 to 9 microns and the human capillaries stained with scarlet red 2 to 5 microns, a great difference; the latter were thinner than a red blood corpuscle (7 microns in diameter). As the fatty content of the vessels is interrupted at some spots, I was able to study the vessel walls very well at these points with the highest power magnification of the microscope. The content is shining red with some yellowish spots. The vessel wall is outlined by dark red sharp incrustations of different size and shape,

7. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922; Technik der mikroskopischen Untersuchung des Nervensystems, ed. 4, Berlin, Julius Springer, 1930.

8. Wislocki, G. B., and Campbell, A. C. P.: Anat. Rec. **67**:177, 1937.

surrounding the red content like a pipe, recognizable by means of the stereomicroscope, which demonstrates the shape of the vessel in space (fig. 6 *A*).

Focusing on the end loops, one can distinguish a cloud of dark reddish purple spots of different shape covering these vessel turns, sometimes leaving the bend like the tail of a comet, sometimes like a swarm of bees spreading in the surface retinal layer (figs. 6 *A* and *B*). They are not distributed like vessels and vary in breadth from 3 to 60 microns or more. They are not artefacts as I assumed when I first saw them. It is not possible to confuse them with the surface precipitates. They are different in size, shape and color. As there

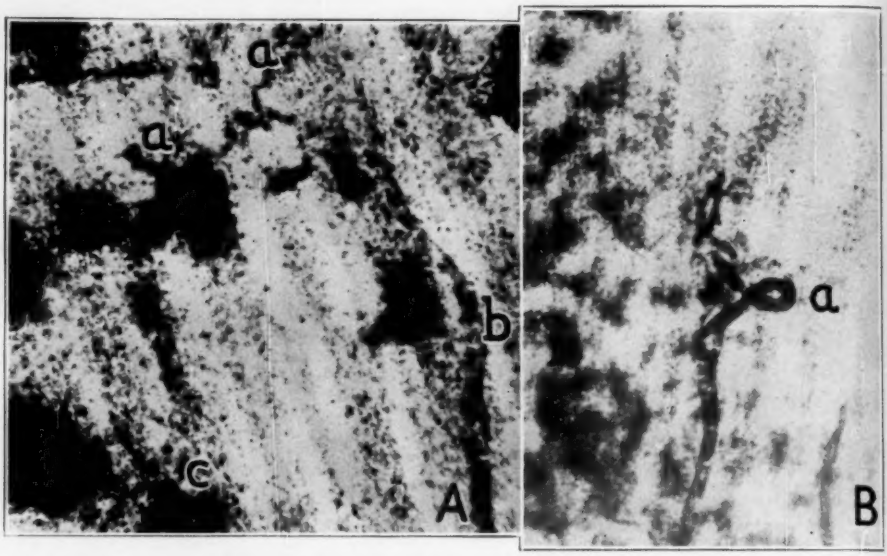

Fig. 6.—*A*, retina of rabbit (stained with scarlet red; high power) fed cholesterol for five months, showing (*a*) comet-shaped tails, (*b*) end loops and (*c*) end loop which is not in the same level. *B*, retina (stained with scarlet red and kept in potassium hydroxide and glycerin [high power]) of rabbit 3, showing the comet-like tail (*a*) from the thick end loops of the retinal vessel (fatty plasma leaving the vessel).

are no lymph vessels (otherwise not proved at all within the retina) and no artefacts, I came to the conclusion that this remarkable appearance represents the fatty external lymph stream of the blood vessel system. As the retinal vessels of the rabbit develop entirely superficially as a membrana vasculosa retinae, it is easy to detect this interesting picture in a rabbit fed cholesterol (for three to six months) within a retina in bulk which has not even been cleared with potassium hydroxide

and glycerin. It seems that the retinal metabolism depends partially on this lymph stream, although the main part of the retinal nourishment is supplied by the choroid. On the other hand, it is impossible for this stream to reach far from the medullated fiber zone. I succeeded in delineating this fatty stained lymph stream twice only.

It is amazing what a regular network is found at the surface of the retinas of kittens (fig. 7). It is easier to separate the retina from the globe in a kitten's eye than in that of a human being. The kitten's retina is much thicker. Wishing to study the vessel system, I used a higher concentration of potassium hydroxide (20 per cent with glycerin) and succeeded in destroying the retinal tissue better, the vessel system becoming clearer in this way. The membrana vasculosa retinae stood

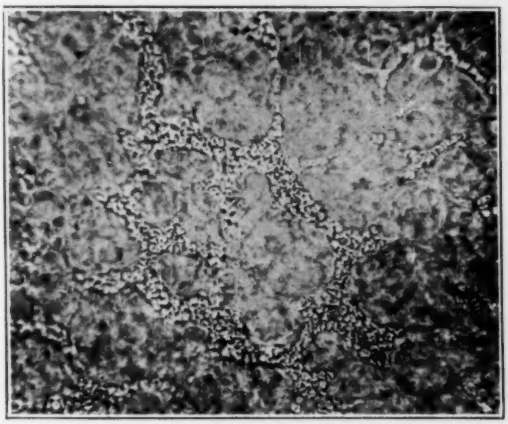

Fig. 7.—Membrana vasculosa retinae superficialis of a kitten retina (unstained).

out sharply (fig. 7); many of the capillaries within the meshwork contained blood corpuscles and the network was extremely regular.

The most interesting way of studying the retina in bulk is, of course, by studying the retina of patients with hyperpiesia. Some of these patients were controlled very carefully ophthalmoscopically. Professor Ballantyne devoted a great deal of time to this work, and we were astonished to find how far reaching are the anatomic changes compared with the ophthalmoscopic ones. Here I present a short survey only, as the details will be found in another paper in connection with the experimental results.

The larger branches show very impressively the fatty infiltration of the vessel walls (fig. 8). Especially in empty pieces of the arteries are these lipoid drops easily recognized (the word lipoid is used here in its broader sense). The arcades are sharply outlined (fig. 9*A*), and

there is no doubt of the existence of real, regular anastomoses. Not too rarely the most beautiful network of the capillaries is spread over a larger retinal area (fig. 9 *B*). The shape of these capillaries is regular at some places and deformed at others, with local widening of the lumen, little spindle-shaped aneurysms and irregular thickening of the wall (fig. 10 *A*). The predominant impression is that of destruction by a grave disease of the vessel system, affecting the smaller vessels even more than the larger ones (fig. 10). The content of the larger vessels, which is often interrupted (fig. 11), is bright red. It seems as if the lipoid dissolved or emulsified in the serum is the

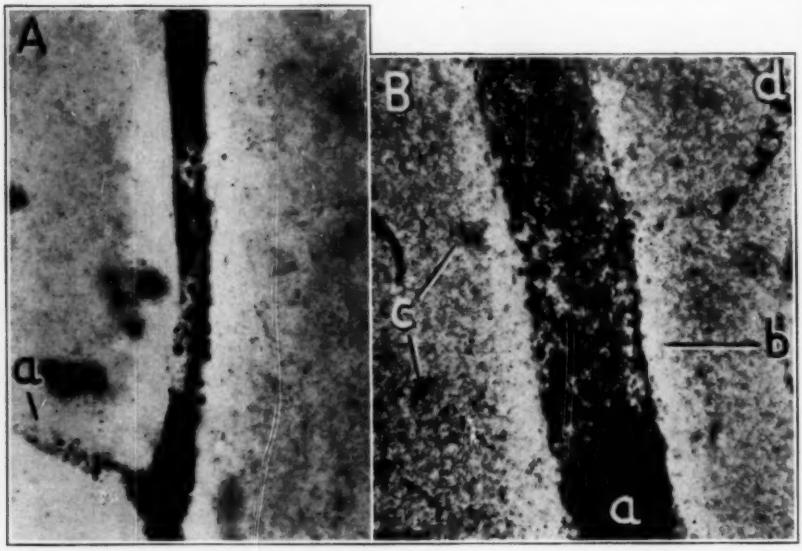

Fig. 8.—*A*, retina (stained with scarlet red), showing fatty plasma stained pinkish red and shining red drops within the vessel wall ([*a*] empty vessel). *B*, specimen (stained with scarlet red), from patient with hypertensive retinopathy showing (*a*) fatty content (plasma), (*b*) fatty incrustation in the vessel wall, (*c*) tiny fatty droplets in groups on the retinal surface and (*d*) smaller vessel.

cause of the positive staining for fat. The coagulation of the blood within the larger vessels causes shrinking at certain spots, leading to empty spaces (fig. 11). However, the smaller vessels and the capillaries show the fatty droplets in the vessel walls only, and these incrustations are formed by darker purple droplets (fig. 9 *B*). I do not know why the greater lipoid areas, as well as the larger fatty drops in the deeper retinal layers, are bright red, while the finer ones in the vessel walls, as well as in the retinal tissue, are dark purple.

In cases of high blood pressure or retinitis albuminuria I found different groups of lipoid drops in different retinal layers. I could study these in unstained pieces of retina also cleared up with potassium hydroxide and glycerin. The highest are tiny groups arranged parallel to the nerve fiber bundles, which were easily recognizable (fig. 10 A). Twenty-five microns deeper there are regular groups of lipoid drops, but these are not at a uniform level. There is often a difference of 20

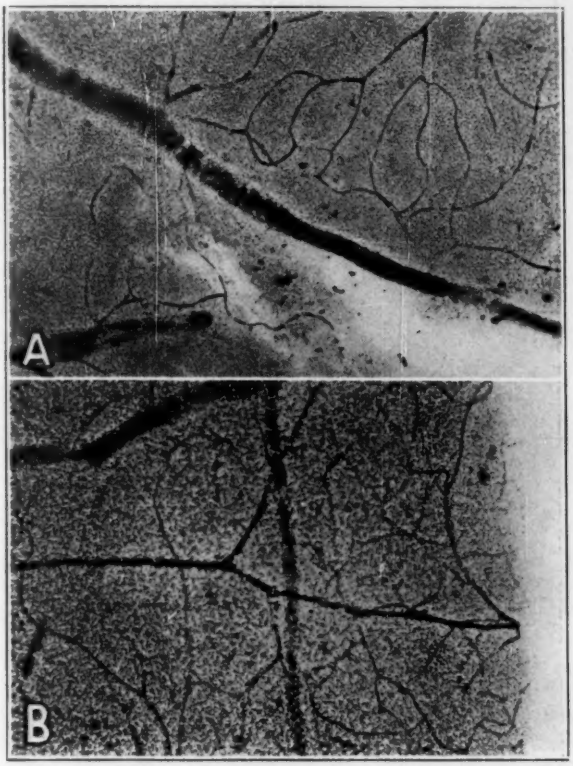

Fig. 9.—Human capillaries, showing (*A*) arcades with fatty walls and (*B*) narrow arcades.

microns between each group of these lipoid drops. A little deeper there are often large structureless fatty drops, surrounded by softened pellucid areas, apparently spots of malnutrition (fig. 10 B). These fatty drops are the deepest incrustations I found in the retina in bulk. In the deeper layers I could not detect any fatty drops by this method.

Finally I want to stress the existence of the narrow retinal meshwork (fig. 9). As the capillaries appear in these preparations they are

too thin to allow the passage of blood corpuscles (2.5 to 5 microns). If these capillaries are to function, they must widen, as a red blood corpuscle has a diameter of 7 microns. The passage even of such a deformed element would be difficult.

I am inclined to think that this meshwork is the reserve vessel system. It is usually collapsed, thin, empty and not visible, but filled with

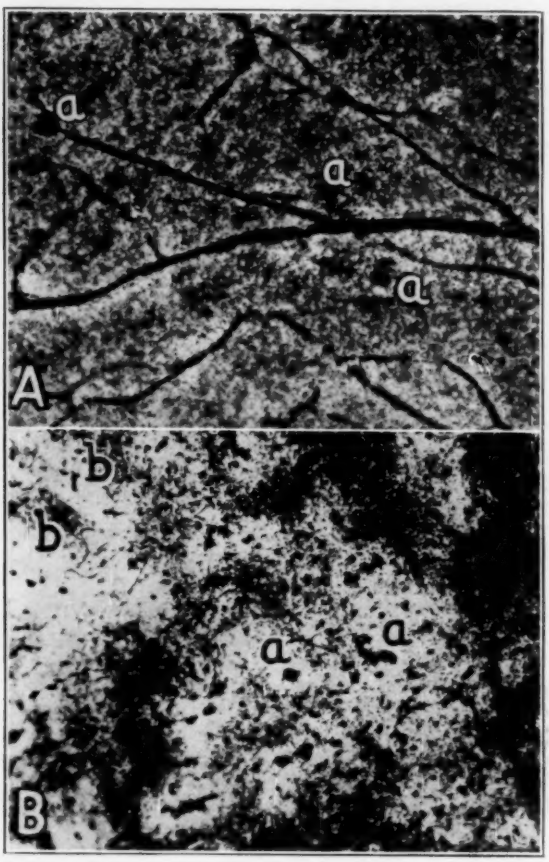

Fig. 10.—*A*, precapillaries and capillaries of very irregular shape, with tiny fatty superficial droplets (*a*) in small groups. *B*, specimen from patient with albuminuric retinopathy, showing a clearing up around the red-stained (scarlet red) fatty drops (*a*), with the irregular capillary loops (*b*).

blood under exceptional circumstances. I am able to prove by means of the slit lamp that such a vessel system exists in the conjunctiva. To control the minute conjunctival vessels a drop of ethylmorphine hydrochloride is administered. The small vessels under observation dilate widely, and a great mass of new vessels appear, which were apparently empty

before. Havlicek (1925-1935), in his Schatzlar thesis, stressed the high importance of these two vessel systems, the functioning one and the reserve system, the latter widening in the case of inflammation and under the influence of histamine. In the extremities arteriovenous anastomoses are observed between arteries and veins without interpolation of the peripheral capillaries, usually slowing the blood stream. These anastomoses can be studied histologically (Schumacher,[9] Clara [10] and Spanner [11]). They are without an elastica interna. The muscular cells are changed into epithelial elements, able to swell and thus occlude the lumen of these vessels and to shrink and thus open the path of the reserve vessel system. Some facts, which are well known to the clinician but not understood from textbook learning, seem to aid Havlicek's theories. It is well known, for example, that a fatty embolism

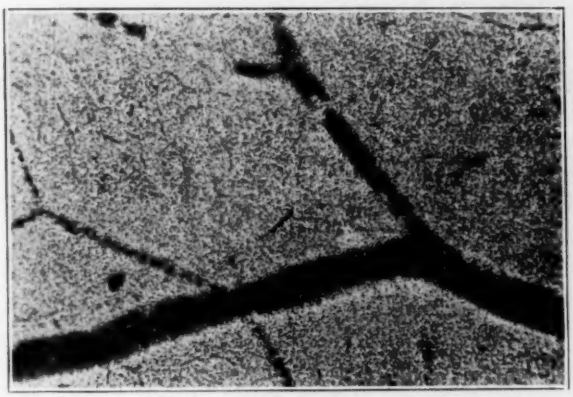

Fig. 11.—Fatty content of larger vessels of human retina (stained with scarlet red).

of the central retinal artery not rarely follows a fracture of the femur. To explain this fact one has to assume, according to Harvey's explanation, that the fatty embolus passes the veins into the heart, follows the pulmonary arteries, then passes through the narrow pulmonary capillaries and reaches the left side of the heart and the arterial system. This seems incomprehensible. Havlicek's assumption of a wider precapillary anastomosis [12] would be a good explanation: a short circuit between pulmonary artery and vein, avoiding the thin capillaries. Such an explanation accounts for the surprising fact that an embolism of the

9. Schumacher, S.: Beitr. z. klin. Chir. **159**:335, 1934.

10. Clara, M.: Anat. Anz. **55**:399, 1922.

11. Spanner, R.: Morphol. Jahrb. **69**:394, 1932.

12. Havlicek, H.: Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1934, p. 195.

central retinal artery has been found after subcutaneous injection of cosmetic paraffin into patients with saddle nose. The assumption that the paraffin particles pass from the absorbing veins to the right side of the heart, through the pulmonary arteries, capillaries and veins into the left side of the heart and then into the carotid artery is very unlikely. Havlicek's theory of the pulmonary short circuit seems probable in these cases.

The idea that a part—perhaps a great part—of the rich and very thin capillary system found in the retina belongs to the reserve vessels, which are normally empty, is worth considering.

SUMMARY OF PART II

Rabbits were fed cholesterol for three to six months. The retina in bulk was stained with scarlet red and cleared with potassium hydroxide and glycerin. The vessel tree is sharply defined. The vascular end loops here appear much thicker than in human retinas. Cloudy deposits could be demonstrated around the hairpin-shaped end loops, which were explained as fatty compounds of the lymph stream leaving the blood vessels. A very narrow blood-filled meshwork at the surface layer of the kitten's retina is described as a membrana vasculosa retinae. In cases of hypertensive retinopathy in human beings a network of very thin capillaries is demonstrated, some of them with destruction of the walls and aneurysmatic widening. Fatty deposits of different shape are proved in different layers of the retina, some of them in a softened cleared up area. Some tiny lipoid droplets at the retinal surface are too small to be recognized ophthalmoscopically. The thin capillary meshwork is assumed to belong partly to the reserve vessel system, which is usually empty.

EPIDEMIOLOGY OF INCLUSION CONJUNCTIVITIS

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Although inclusion conjunctivitis in the infant was defined as an entity as early as 1911 by Lindner,[1] general textbook recognition of its widespread occurrence and of its importance as one of the types of ophthalmia neonatorum did not obtain until recently. There was, furthermore, a delay in the identification of the not uncommon infection of the adult with that of the infant, although a nontrachomatous conjunctivitis with epithelial cell inclusions epidemic among bathers in certain public pools was recognized by Huntemüller and Paderstein[2] in 1913. This delay in identifying the disease in the infant and that in the adult may have been due to differences in clinical appearance, the latter disease being characteristically follicular and milder than the former, which is an acute papillary conjunctivitis. At present, however, as a result of the filtration experiments of Gebb,[3] Botteri,[4] Thygeson,[5] Tilden and Gifford[6] and Julianelle, Harrison and Lange,[7] inclusion con-

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From the Department of Ophthalmology, Columbia University, College of Physicians and Surgeons, and the Institute of Ophthalmology of the Presbyterian Hospital.

1. Lindner, K.: Gonoblennorrhöe, Einschlussblennorrhöe und Trachom, Arch. f. Ophth. **78**:245, 1911.

2. Huntemüller and Paderstein, R.: Chlamydozoen-Befunde bei Schwimmbadconjunctivitis, Deutsche med. Wchnschr. **39**:63, 1913.

3. Gebb, H.: Experimentelle Untersuchungen über die Beziehungen zwischen Einschlussblennorrhöe und Trachom, Ztschr. f. Augenh. **31**:475, 1914.

4. Botteri, A.: Klinische experimentelle und mikroskopische Studien über Trachom, Einschlussblennorrhöe und Frühjahrskatarrh, Klin. Monatsbl. f. Augenh. **50**:653, 1912.

5. Thygeson, P.: The Etiology of Inclusion Blennorrhea, Am. J. Ophth. **17**: 1019, 1934.

6. Tilden, E. B., and Gifford, S. R.: Filtration Experiment with the Virus of Inclusion Blennorrhea, Arch. Ophth. **16**:51 (July) 1936.

7. Julianelle, L. A.; Harrison, R. W., and Lange, A. C.: Studies on Inclusion Blennorrhea: III. Experimental Considerations on the Etiology, Am. J. Ophth. **21**:1230, 1938.

junctivitis is recognized as an etiologic entity caused by a filtrable virus. Although there is a specific treatment for it with sulfanilamide and its derivatives,[8] the virus has not yet been cultivated and little is known of its properties. Nor is the epidemiology of the infection thoroughly understood as yet, although early workers[9] recognized the birth canal of the mother as the source of the disease in the infant and indicated its probable venereal nature by demonstrating the virus in cases of nongonococcic urethritis in the male.

In spite of several studies on the genitourinary infection, much is yet to be learned of its frequency, distribution, localization and clinical importance and of its role in epidemics of inclusion conjunctivitis in children and in adults. The following study on epidemiology is a continuation of a study made at the University of Iowa in 1936 by Thygeson and W. L. Mengert.[10]

FREQUENCY AND CHARACTERISTICS OF INCLUSION CONJUNCTIVITIS IN NEW YORK CITY

The clinical characteristics of the inclusion conjunctivitis seen in New York city are essentially those of the disease previously observed in Iowa. Of the 51 patients in the series, 39 were infants, 3 were children and 9 were adults. The disease in infants was a papillary conjunctivitis of varying severity, 4 patients having a reaction severe enough to produce a pseudomembrane but none showing scarring. The disease untreated ran a clinical course of at least three months, the average duration being about four and a half months. The 3 children and the 9 adults showed predominant follicular hypertrophy. Local treatment with silver nitrate or other ordinary antiseptics failed to influence the course of the disease, but sulfanilamide given by mouth in 18 cases[8] and 5 per cent sodium sulfathiazole (the sodium salt of 2-[paraaminobenzenesulfonamido]-thiazole) ointment used in 6 cases[11] effected rapid cures.

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8. Thygeson, P.: Treatment of Inclusion Conjunctivitis with Sulfanilamide, Arch. Ophth. **25**:217 (Feb.) 1941.

9. (*a*) Halberstaedter, L., and von Prowazek, S.: Ueber Chlamydozoenbefunde bei Blennorrhea neonatorum non gonorrhoica, Berl. klin. Wchnschr. **46**: 1839, 1909; (*b*) Ueber die Bedeutung der Chlamydozoen bei Trachom und Blennorrhöe, ibid. **47**:661, 1910. (*c*) Heymann, B.: Ueber die Fundorte der Prowazekschen Kärperchen, ibid. **47**:663, 1910. Thygeson.[5] Thygeson and Mengert.[10]

10. Thygeson, P., and Mengert, W. L.: The Virus of Inclusion Conjunctivitis, Arch. Ophth. **15**:377 (April) 1936.

11. Thygeson, P., and Stone, W., Jr.: The Treatment of Inclusion Conjunctivitis with Sulfathiazole Ointment, to be published.

As indicated in table 1, 25 cases of inclusion blennorrhea occurred in the Sloane Hospital for Women between July 1936 and May 1941, constituting an incidence of 0.34 per hundred births. This is in contrast with the Iowa series,[10] in which the incidence was 0.8 per cent. In view of the venereal nature of the infection the higher incidence in Iowa may have been related to the higher rate of illegitimacy, which probably indicates greater sexual promiscuity in the mothers.

METHODS OF DEMONSTRATING THE VIRUS

Two methods of demonstrating the virus of inclusion conjunctivitis were employed in this study: (1) the microscopic demonstration of inclusion bodies and their components, the free elementary and the initial bodies, in epithelial scrapings from the lesions and (2) the production of a characteristic follicular conjunctivitis in baboons (fig. 1),

TABLE 1.—*Incidence of Inclusion Blennorrhea in Babies Born at the Sloane Hospital for Women*

Year	Number of Births (Ward Patients)	Cases of Inclusion Blennorrhea (Ward Patients)	Number per 100 Births
1936 (last 4 months)	517	3	0.58
1937	1,634	6	0.36
1938	1,548	2	0.13
1939	1,517	9	0.59
1940	1,495	3	0.20
1941 (first 4 months)	498	2	0.40

in material from which the inclusion bodies could be demonstrated regularly (fig. 2).

The baboon test was found to be more sensitive than the microscopic test, but both were reliable when sufficient material for testing was obtained. In the baboon test too much time must not be allowed to elapse before inoculation, as the virus does not survive long, particularly at room temperature. The microscopic test requires a trained observer familiar with the various types of artefacts and pseudoinclusions which occasionally simulate inclusion bodies and free elementary bodies. In this connection it should be emphasized that the inclusion bodies of inclusion conjunctivitis are indistinguishable from those of trachoma and that experimental trachoma in the baboon cannot be differentiated from experimental inclusion conjunctivitis except by its longer duration. These similarities, however, do not constitute serious sources of confusion, since trachoma in the human being can be readily differentiated clinically and does not enter into the picture of the genitourinary disease.

In working with the genitourinary disease we have kept in mind the possibility of confusion of the virus with that of lymphogranuloma

Fig. 1.—Drawing of experimental inclusion conjunctivitis in the baboon.

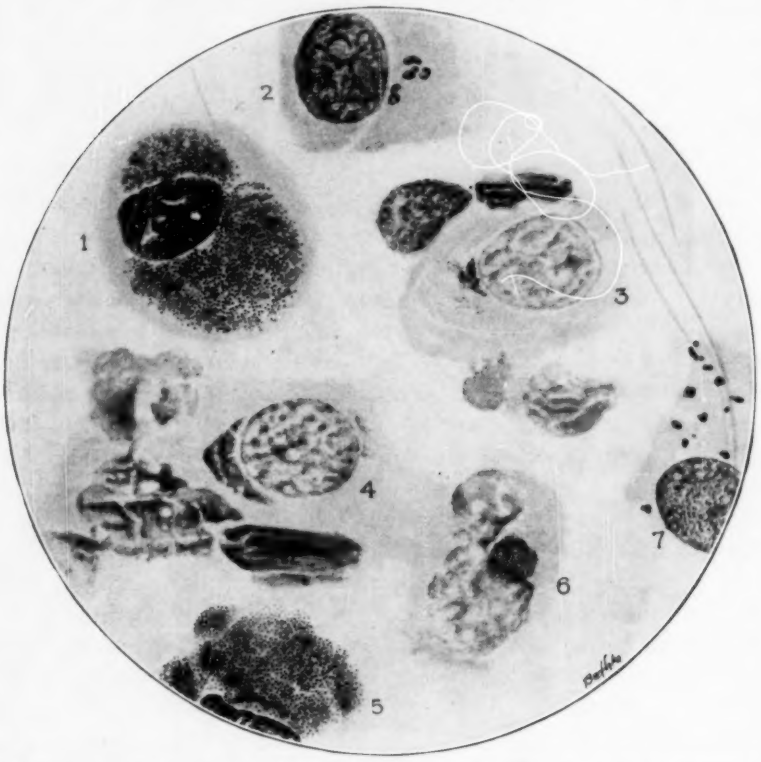

Fig. 2.—Drawing of inclusion bodies from the conjunctiva of a baboon with experimental inclusion conjunctivitis (Giemsa stain).

venereum, which may occur in the genitourinary tract and is similar to the virus of inclusion conjunctivitis in size, staining properties and the morphologic variation of its elementary bodies.[12] Although the free elementary and the initial bodies of the two diseases are in our opinion indistinguishable (fig. 3), there should be little danger of error, since the inclusions, though similar, are not identical and affect different cells. The inclusion body of inclusion conjunctivitis affects only epithelial cells, while the inclusion body of lymphogranuloma venereum

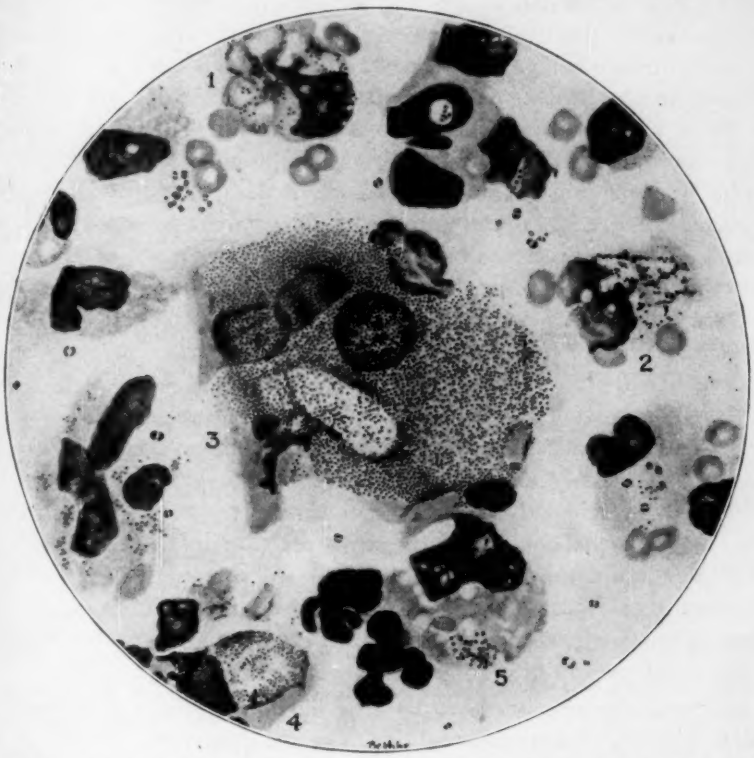

Fig. 3.—Drawing of inclusion bodies, free elementary bodies and initial bodies of lymphogranuloma venereum (mouse brain impression smear; Giemsa stain).

affects primarily mononuclear cells.[13] So far as we have been able to determine, inclusions of lymphogranuloma venereum have not been

12. Findlay, G. M.; Mackenzie, R. D., and MacCallum, F. O.: A Morphological Study of the Virus of Lymphogranuloma Inguinale (Climatic Bubo), Tr. Roy. Soc. Trop. Med. & Hyg. **23**:183, 1938.

13. Van Rooyen, C. E., and Rhodes, A. J.: Virus Diseases of Man, London, Oxford University Press, 1940, p. 181.

found in epithelial cells in the genitourinary tract, although they have been reported in epithelium in tissue cultures.[14] We failed to find inclusion bodies in epithelial cells at biopsy or in epithelial scrapings from 1 patient with proved primary ocular lymphogranuloma venereum and 2 baboons with experimental ocular infection.

In an effort to eliminate the virus of lymphogranuloma venereum as a factor in the baboon test, each animal in which experimental inclusion conjunctivitis developed was given an intradermal injection of Frei antigen of human origin and of known potency. None of the baboons reacted positively. However, although the reaction to the Frei test in the human being is considered to be a reliable index of infection,[15] its value in the baboon has been in question. In order to determine this value and to compare the two experimental diseases in monkeys and baboons, we attempted to produce experimental ocular lymphogranuloma venereum in these animals. Dr. M. Sanders, of this institution, provided a strain of the virus of lymphogranuloma venereum in the form of mouse brain emulsion, and this was used for conjunctival and subconjunctival inoculation. In spite of the fact that the virus was of high titer for mice and could be readily demonstrated in the form of elementary bodies in the emulsion, none of 3 Macacus rhesus monkeys became infected. In the 2 baboons inoculated, however, there developed mild papillary conjunctivitis with pseudoptosis, without regional adenopathy and without systemic symptoms. In the first baboon the conjunctivitis healed spontaneously after a duration of six weeks; in the second the conjunctivitis is still active at the time of writing, two weeks after inoculation. The first baboon gave a negative reaction to the Frei test four weeks after inoculation, when the virus was still present, as demonstrated by intracerebral inoculation of mice with conjunctival scrapings. The failure of cutaneous allergy to develop in the baboon is probably due to the failure of the infection to become generalized.

Although there appeared to be little likelihood of our confusing the clinical picture of experimental inclusion conjunctivitis with that of experimental ocular lymphogranuloma, 6 baboons with experimental inclusion conjunctivitis derived from genitourinary sources were tested for the presence of the virus of lymphogranuloma venereum by mouse brain inoculations with conjunctival scrapings. In no instance did infection of the mouse result.

Table 2 shows some of the essential differences between the viruses of trachoma, inclusion conjunctivitis and lymphogranuloma venereum.

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14. Nauck, E. G., and Malamos, B.: Ueber Erregerfunde bei Lymphogranuloma Inguinale, Arch. f. Schiffs- u. Tropen-Hyg. **41**:537, 1937.

15. Van Rooyen and Rhodes,[13] p. 189.

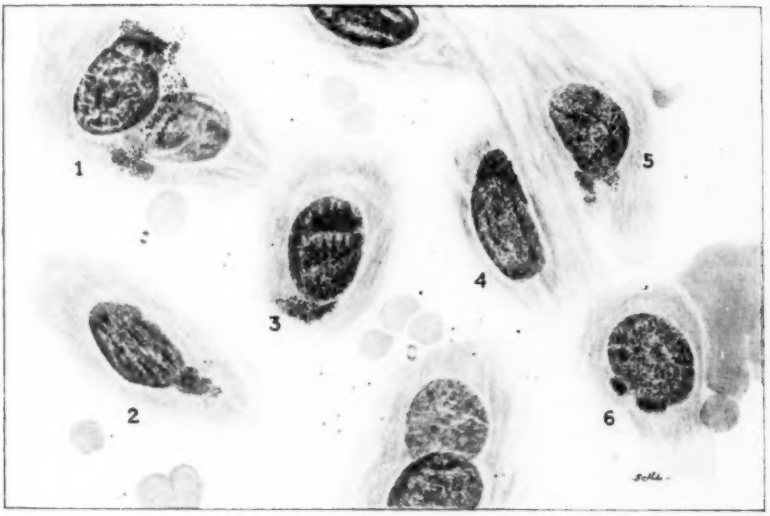

Fig. 4.—Inclusion bodies in cervical scrapings from mothers of babies with inclusion blennorrhea (Giemsa stain).

UNIV. OF MICH.

LOCALIZATION OF THE VIRUS OF INCLUSION CONJUNCTIVITIS

In Conjunctival Material.—There has been no difficulty in demonstrating the virus either microscopically in the form of inclusion bodies or by baboon inoculation in conjunctival material in cases of early involvement or in cases in which the infection was active even though of several months' duration. The number of inclusion bodies was much larger in material from newborn infants than in material from adults and the bodies were always more numerous in smears from the lower tarsal conjunctiva than in smears from the upper conjunctiva.

In Cervical Scrapings from Mothers of Babies with Inclusion Blennorrhea.—There was no difficulty in demonstrating the virus in cervical

TABLE 2.—*Differences Between the Viruses of Trachoma, Inclusion Conjunctivitis and Lymphogranuloma Venereum*

	Trachoma	Inclusion Conjunctivitis	Lymphogranuloma Venereum
Inclusion bodies.....	Cytoplasmic in epithelial cells	Cytoplasmic in epithelial cells	Cytoplasmic in mononuclear cells; not yet demonstrated in ocular epithelium
Free bodies.....	Free elementary and initial bodies	Free elementary and initial bodies	Free elementary and initial bodies
Carbohydrate matrix....	Present in all mature inclusions	Present in all mature inclusions	Not demonstrated
Cutaneous allergy.....	Not demonstrated	Not demonstrated	Demonstrated by Frei test
Localization.....	Eye only	Genitourinary tract and eye	Genitourinary tract, joints and eye
Complement fixation....	Not demonstrated	Not demonstrated	Reaction positive
Pathogenicity.....	Conjunctiva, monkeys and apes only	Conjunctiva, monkeys and apes only	Most laboratory animals susceptible to infection by various routes
Sensitivity to sulfanilamide.....	+	+	+

material taken from the mothers of babies with inclusion blennorrhea at the time of their discharge from the hospital, ten to twelve days after delivery. Baboon inoculation proved more sensitive than the microscopic test, positive results being obtained with it in 10 of the 13 cases while in only 7 of the 13 was the virus demonstrated microscopically. In none of the latter cases were the inclusion bodies numerous. Figure 4 illustrates some of the inclusions found in these cases. Free elementary bodies were also found in some cases but were not so numerous as in the Iowa case previously reported in which they were present in enormous numbers.

Table 3 outlines the venereal disease history of the mothers of the babies with inclusion blennorrhea. It is of interest that of the 38 only 1 was known to have gonorrhea and only 2 syphilis, while none had clinical signs of lymphogranuloma venereum. The reaction to the Frei

TABLE 3.—*Venereal Disease History of Mothers of Babies with Inclusion Blennorrhea*

Number	Race	Name	History of Abnormal Discharge During Pregnancy	Venereal Disease History	Smear for Gonococci and Wassermann Test	Marital Status
1	N	C. L.	Slight white spotting discharge; no burning on urination	Denied gonorrhea, syphilis; no history of extramarital sexual relations; some premarital sexual relations	Negative	Married
2	N	E. B.	Slight white spotting discharge after baby was born; none before; no burning on urination	Denied gonorrhea, syphilis; no history of premarital or extramarital sexual relations; salpingitis and cystic ovary discovered after baby was born	Negative	Married
3	W	M. J.	No discharge	Denied gonorrhea, syphilis; cyst of ovary.....	Wass.: Chol. +++, alc. neg.; gon. neg.	Married
4	N	C. J.	No history obtainable.....	.....	Negative	Married
5	..	W.	No history obtainable			
6	W	J. C.	No history obtainable.....	.....	Negative	Married
7	N	A. S.	Antepartum yeast vaginitis.....	Denied gonorrhea, syphilis; no history of extramarital or premarital sexual relations	Negative	Married
8	N	A. R.	No history	.....	Negative	Husband deserted before birth of baby
9	N	D. B.	No history	No history	Negative	Married
10	N	M. B.	No history	No history	Negative	Unmarried
11	N	E. F.	No history	No history	Negative	Common law marriage
12	N	D. R.	Whitish discharge for one year preceding this pregnancy; no yeast, trichomonads or gonococci	No history	Negative	Married
13	..	B. P.	No history			
14	N	L. M.	No discharge	Husband had slight urethral discharge, lasting five days, 2 weeks after baby was born; no burning, no gonococci; denied ever having had gonorrhea	Negative	Married
15	W	J. O.	Slight fetid discharge following pregnancy; no hemolytic streptococci or gonococci	Husband had gonorrhea 20 years before birth of baby; no discharge since; no history of extramarital relations of either partner	Negative	Married
16	W	G. H.	Slight discharge after baby was born	Denied gonorrhea, syphilis; husband had gonorrhea a few years before; denied extramarital relations	Negative	Married
17	N	L. F.	8 years before baby was born patient had slight discharge for 1 year; no pad necessary, no burning, slight itching, cleared with douches; considerable white discharge after baby was born	4+ Wassermann reaction in 1937, with antisyphilitic treatment (baby born in 1939); husband, [illegible] Wassermann reaction, with treatment	.....	Married
18	W	A. D.	Slight white spotting discharge for several months prior to pregnancy; no burning or itching	Denied gonorrhea, syphilis, extramarital relations	Negative	Married
19	N	L. B.	Slight white discharge since childhood; no burning or itching	Denied gonorrhea, syphilis; said husband had never had discharge; no extramarital relations	Negative	Married

20	W	M. B.	No history		Negative	Single at time of delivery
21	N	E. P.	Slight amount of purulent material expressed from urethra just prior to delivery; no gonococci or trichomonads		Negative	Married
22	W	N. D.	No discharge	Denied gonorrhea, syphilis, extramarital relations; no history of venereal disease in husband	Negative	Married
23	W	H. L.	No history		Negative	Married
24	W	G. W.	No history		?	Married
25	N	A. Y.	Infection with Trichomonas vaginalis just before pregnancy		Negative	Married
26	W	A. B.	No abnormal discharge	Wassermann reaction 1+, 10/25/39		Married
27	W	M. D.	No abnormal discharge	Denied syphilis, gonorrhea, extramarital relations; husband denied gonorrhea, syphilis, discharge	Chol. 3+ (1937); Kline reaction negative (1940); baby born in 1940; no gonococci	Married
28	N	K. R.	No history	History of inflamed ovary 4 years before this pregnancy; syphilis 3½ years before	Negative	Married
29	W	M. T.	No history		No smear or test	Married
30	..	H. H.	Yeast vaginitis before pregnancy		Negative	Married
31	W	K. N.	No history	No history of venereal disease in either partner	Negative	Married
32	..	G.	No history			
33	W	R.	No discharge	Husband had moderate nonspecific urethral discharge, lasting 4 to 6 weeks, 3½ years before birth of baby; no burning, no discharge since	Negative	Married
34	..	A. S.	Vaginal discharge most of adult life, worse during pregnancy; had to wear pad; no gonococci	Husband had gonorrhea with discharge 5 years before birth of child; no discharge since	Negative	Married
35	N	P.	Slight white spotting discharge during pregnancy; no gonococci	Husband and patient denied gonorrhea, extramarital relations	Negative	Married
36	W	A.	No discharge	Four months previous to birth of child had intercourse with man whom she says had syphilis; positive Wassermann reaction during pregnancy and gonococci in urethra 6 days after delivery (no discharge); inclusion bodies in material from cervix; no inclusion bodies in urethral scrapings; Frei reaction negative	Negative	Single
37	..	J. J.	No discharge	Husband had gonorrhea some years before; no history of recent discharge; he also had positive Wassermann reaction at time of birth of child; patient had negative Wassermann reaction; smears negative for gonococci	Negative	Married
38	W	E. C.	No discharge	Husband had profuse burning discharge 9 years before birth of child; urine cloudy since; no discharge since; patient denied gonorrhea, syphilis; Frei reaction negative	Negative	Married

test was found to be negative in the only 2 mothers tested. Although 14 of the 26 mothers questioned complained of slight or moderate vaginal discharge during pregnancy, this cannot be considered as unusual or significant. On the other hand, the postpartum morbidity of the mothers whose babies had inclusion blennorrhea, as indicated in table 4, was 8 of 38, or 21 per cent, a figure significantly higher than the 8.7 per cent average morbidity at the Sloane Hospital for Women during the same five year period. The possibility that the virus of inclusion conjunctivitis has a role in the production of postpartum febrile complications will be considered in a subsequent study.

Lindner [16] concluded that the genital infection in the female is of relatively short duration, since in his experience there was never more than one child in a family affected. In the Iowa series there was no evidence of the infection of a second child. Table 5 outlines the data on 12 of the mothers in the present series, each of whom had more than one child and at least one child with inclusion blennorrhea. While proved inclusion blennorrhea occurred in only one child in each family, there were 4 families in which one other child showed a conjunctivitis which could well have been inclusion blennorrhea as judged by time of onset and clinical course although a microscopic demonstration of the inclusion bodies was not made. Since inclusion blennorrhea is for practical purposes the only conjunctivitis of the newborn which appears from the fifth to the tenth day after birth and runs a clinical course of several months, it may be justifiable to assume that the conjunctivitis of the other child in these families was inclusion blennorrhea and to state, on the basis of that assumption, that the virus of inclusion conjunctivitis may conceivably persist in the female genital tract for as long as three or four years.

It is of interest in this connection that Hamburger [17] reported inclusion blennorrhea in 2 children of one family born two and a half years apart and that Julianelle and Lange [18] likewise reported infection of 2 children in one family born two and a half years apart. That inclusion blennorrhea does not develop in all babies whose mothers carry the infection is indicated by the fact that the disease developed in only 1 of a pair of twins reported on by Howard.[19]

As in the Iowa series the virus was found to be localized in the cervix. There was no evidence of urethritis except in the 1 case of

16. Lindner, K., in Berens, C.: The Eye and Its Diseases, Philadelphia, W. B. Saunders Company, 1936, p. 442.

17. Hamburger, F.: Die Rolle des Einschlussvirus am Auge des Neugeborenen und am Genitale der Frau, Arch. f. Ophth. **133**:90, 1934.

18. Julianelle, L. A., and Lange, A.: Studies on Inclusion Blennorrhea: Clinical and General Observations, Am. J. Ophth. **21**:890, 1938.

19. Howard, W. A.: Inclusion Blennorrhea, J. Pediat. **12**:139, 1938.

Table 4.—Complications of Pregnancy and Labor, Not Including Those Involving Length of Labor, Premature Rupture of Membrane or Dis-

TABLE 4.—*Complications of Pregnancy and Labor, Not Including Those Involving Length of Labor, Premature Rupture of Membrane or Discharge from Vagina*

Number	Case	Antepartum Status	Labor	Postpartum Status
1	C. L.	Normal conditions	Normal	No rise in temperature
2	E. B.	Fecal impaction	Normal	No rise in temperature
3	M. J.	Secondary anemia (hemoglobin 67%, red cells 3,600,000)	Normal	No rise in temperature
4	C. D.	Normal conditions	Normal	Chronic endometritis with infection of upper respiratory tract 5th to 12th day post partum
5	W.	Normal conditions	Normal	No rise in temperature
6	J. C.	Normal conditions	Normal	No rise in temperature
7	A. S.	Normal conditions	Normal	No rise in temperature
8	A. R.	Normal conditions	Normal	Unexplained fever with temperature 100 F. for 3 days after delivery; no hemolytic streptococci or gonococci found on vaginal culture
9	D. B.	Normal conditions	Normal	Undiagnosed fever with temperature 100 to 101 F. from 2d to 6th day post partum; vaginal smear negative for gonococci and very small gram-positive and gram-negative bacilli
10	M. B.	1937, normal conditions	Normal	Undiagnosed fever with temperature to 101 F. for 4 days; no organisms found on vaginal culture
11	E. F.	1939, normal conditions 1933, no history 1937, pernicious vomiting	....	No rise in temperature No rise in temperature
12	D. R.	Hypertensive toxemia of pregnancy	Premature	No rise in temperature
13	B. P.	No history		
14	L. M.	Normal conditions	Normal	No rise in temperature
15	J. O.	Mild toxemia of pregnancy	Normal	Temperature to 100 F. on 4th day
16	G. H.	Normal conditions	Normal	No rise in temperature
17	L. F.	Normal conditions	Normal	Acute puerperal endometritis; temperature between 100 and 101 F. for 3 weeks post partum; no hemolytic streptococci or gonococci in vaginal culture
18	A. D.	Slight pneumonitis during pregnancy	Normal	No rise in temperature
19	L. B.	Normal conditions	Normal	No rise in temperature
20	M. B.	Normal conditions	Normal	No rise in temperature
21	E. P.	Normal conditions	Normal	No rise in temperature
22	N. D.	Pernicious vomiting	Uterine inertia	No rise in temperature
23	H. L.	Normal conditions	Normal	Puerperal infection; temperature 100.4 for 3 days; not delivered in this hospital
24	G. W.	Normal conditions	Normal	Temperature spiked to 100 F. on 4th day post partum for 1 day
25	A. Y.	Normal conditions	Normal	No rise in temperature
26	A. B.	Normal conditions	Normal	No rise in temperature
27	M. D.	Normal conditions	Normal	No rise in temperature
28	K. R.	Normal conditions	Premature (at 36 weeks)	Temperature 101 F. on 2d day post partum, with a slightly foul lochia; normal on following day
29	M. T.	1934, history unknown; 1937, normal conditions	Normal	No rise in temperature
30	H. H.	Normal conditions	Normal	No rise in temperature
31	K. N.	Normal conditions	Normal	No rise in temperature
32	G.	Normal conditions	Normal	No rise in temperature
33	R.	Normal conditions	Normal	No rise in temperature
34	A. S.	Normal conditions	Normal	No rise in temperature
35	L. P.	Normal conditions	Premature	No rise in temperature
36	A.	Normal conditions	Normal	No rise in temperature
37	J. M.	Normal conditions	Normal	No rise in temperature
38	E. C.	Normal conditions	Normal	Six weeks post partum patient had pain in lower part of abdomen with chills; temperature of 101 F. for 1 day; cervical scraping at this time showed initial bodies and free elementary bodies

gonorrhea in which gonococci but no inclusions were demonstrated in urethral smears. Epithelial scrapings from the vagina and vulva were not taken consistently, but in such scrapings as were taken from these sites no inclusion bodies were demonstrated. Up to the present time we

TABLE 5.—*Pregnancy Records of Mothers of Siblings with Ophthalmia Neonatorum*

No. of Case	Name	Number of Children, With Dates of Birth	Ophthalmia Neonatorum in These Children
1	C. L.	10/ 2/36	Inclusion conjunctivitis
		4/22/39	None
3	M. J.	11/ 5/36	Inclusion blennorrhea
		7/ 5/38	None
		6/14/40	None
9	D. B.	7/18/37	Inclusion blennorrhea
		3/27/38	None
10	M. B.	3/23/37	Inclusion blennorrhea
		6/14/39	Slight purulent discharge began 9th day after birth (left eye), lasted 3 months; no organism found; scrapings not taken
11	E. F.	1/18/30	None
		7/22/31	None
		12/ 5/33	Purulent discharge from both eyes began 8th day, had not stopped at discharge; scrapings not taken; cultures negative
		1/23/37	Inclusion blennorrhea
16	G. H.	2/21/38	None
		8/17/39	Inclusion blennorrhea
19	L. B.	1932	None
		2/13/39	Inclusion bennorrhea
21	E. P.	1/ 4/38	Discharge started on 10th day (both eyes); cultures not made; scrapings not taken
		12/12/39	Inclusion blennorrhea
25	A. Y.	1/ 4/39	None
		9/ 2/40	Inclusion blennorrhea
27	M. D.	1918, 1921, 1925, 1937, 1938	None
		1940	Inclusion blennorrhea
28	K. R.	1923, 1925	None
		1940	Inclusion blennorrhea
29	M. T.	1934	Acute purulent conjunctivitis developed 7th day; not cleared on discharge; no diplococci; no scrapings taken
		1937	None
		1938	Inclusion blennorrhea
30	H. H.	1937, 1938 and 1939	None
		1940	Inclusion blennorrhea

have been able to locate the virus, as indicated by the presence of epithelial cell inclusions, only in the region of the external os of the cervix. This fact agrees with our previous findings and with the findings of Braley,[20] who in a study of biopsy specimens found the inclusions limited to a narrow ring of transitional epithelium just within the external os.

20. Braley, A. E.: Inclusion Blennorrhea, Am. J. Ophth. **21**:1203, 1938.

In Urethral Material from Fathers of Babies with Inclusion Blennorrhea.—Seven of the 12 fathers who were interviewed told of having had a urethritis of some sort at some time in their lives. Most of the 12 admitted sexual promiscuity before marriage, and some, after marriage.

Two histories had special significance and reliability, since they were obtained from physicians whose only babies had inclusion blennorrhea. The first physician gave a history of a low grade nonspecific urethritis, in the discharge of which gonococci could not be found, which occurred three and a half years prior to the birth of the child and lasted five to six weeks. The second, a Negro, stated that prior to the birth of his child he had never had signs or symptoms of urethritis but that two weeks after his wife returned from the hospital he had a mild and transient urethral discharge which did not contain gonococci.

A third history is of particular interest in connection with the probable venereal transmission of the infection. In a baby with inclusion blennorrhea observed at the University of Iowa hospital in 1936 but not previously reported on, gonococcic vaginitis developed on the twelfth day after birth. The mother was found to have gonococci in the cervix, and the virus of inclusion conjunctivitis was demonstrated in cervical scrapings both microscopically and by baboon inoculation. The father was found to have active urethritis in the discharge of which gonococci and free elementary bodies were demonstrated. Although baboon inoculation was not done, the number of free elementary and initial bodies was such as to make reasonably certain a diagnosis of infection due to the virus of inclusion conjunctivitis. It is interesting that at the end of the sixth week the gonococcic infection in the baby spread from the vagina to the eyes and that both inclusions and gonococci could then be demonstrated in epithelial scrapings.

Three of the 12 fathers interviewed denied having had urethral difficulty at any time, a fact which if the histories can be relied on indicates that the husband of an infected woman may escape infection or that the disease in the male may sometimes be subclinical. That the latter hypothesis is a distinct possibility was indicated by our recent experience in demonstrating the virus by baboon inoculation in the case of a symptom-free man who was examined because of known exposure to a gonorrhea-infected prostitute. Three weeks after the first demonstration of the virus a second baboon inoculation with urethral scrapings gave positive results even though no symptoms were present.

In Cervical Scrapings from Nonpregnant Women.—Tables 6 and 7 outline the results of cervical examination for the virus of inclusion conjunctivitis of 184 nonpregnant women with various gynecologic conditions.[21] It will be seen that of the 131 women whose tests for

21. Dr. Richard C. Young, of Columbia University, and Dr. Michael Wishengrad, of the New York City Department of Health, provided the cases for this study.

TABLE 6.—*Cases of Nongonorrheal Cervicitis in Which Cervical Scrapings Were Examined and Baboon Inoculation Was Done*

Gynecologic Condition	No. of Cases	Erosion of Cervix	Discharge	Number of Cases in Which Virus of Inclusion Conjunctivitis Was Demonstrated		Results Negative
				Microscopic Examination of Scrapings	Baboon Inoculation	
Antepartum cervicitis	12	Slight	Slight	0	0	12
Cervicitis due to Trichomonas vaginalis	13	Slight to moderate	Slight to great	0	0	13
Postpartum cervicitis (1 to 6 months)	8	Slight to moderate	Slight to moderate	0	1	7
Chronic pelvic inflammatory disease	78	Slight to severe	Color, white to yellow; consistency, watery to thick and mucopurulent; amount, slight to great	Two with large number of elementary bodies in smear	1 (Not same case as that in column on left)	75
Sterility.....	3	No thickening of tubes	Slight to moderate	0	0	3
Vaginal discharge without trichomonas vaginitis or chronic pelvic inflammatory disease	15	Slight	Slight to moderate	1	1 (case from column on left)	14
Pelvic inflammatory disease	1	None	Great	0	0	1
Pelvic inflammatory disease with positive Frei reaction	1	Slight	Moderate	0	0	1

TABLE 7.—*Data on Five Cases (of Fifty-Three Cases of Gonorrhea in Women) in Which the Virus of Inclusion Conjunctivitis Was Demonstrated in Cervical Scrapings*

No.	Name	Cervical Scrapings	Results of Baboon Inoculation	Comment
1	M. O.	Many gonococci; many free elementary bodies	Negative on 11th day, positive on 18th day after inoculation; many well formed inclusion bodies found	Patient from Bellevue Hospital gynecologic clinic; negative Frei reaction
2	S.	Many gonococci; no inclusion or elementary bodies	Positive; well formed inclusion bodies	Patient, aged 19, delinquent, from public health venereal disease clinic; slight white discharge; gonococci in both urethra and cervix
3	D. R.	Few gonococci; no inclusion or elementary bodies	Positive	Patient from public health venereal disease clinic
4	E. W.	Many gonococci; inclusion bodies in cervix, not in urethra	Negative	Patient from public health venereal disease clinic; history of inflamed tubes 2 years before last exposure; 1 month before examination profuse vaginal discharge; contact had gonococcic urethritis; physical examination showed thickening of left tube; negative Frei reaction
5	G.	Many gonococci and elementary bodies	Inoculation not done	Patient from Iowa City

gonococci gave negative results, the tests of 5 for the virus of inclusion conjunctivitis gave positive results. Two of these had chronic pelvic inflammatory disease and the remaining 3 cervicitis with a vaginal discharge in which Trichomonas vaginalis was not found and which was not accompanied with any evidence of chronic pelvic inflammatory disease. These 5 cases are herewith reported:

CASE 1.—S. R. after a three day labor, premature rupture of the membranes and a cesarean section had acute cervicitis, with Streptococcus haemolyticus demonstrable on culture. She also had pelvic thrombophlebitis. Afterward she had a white discharge sufficient to cause spotting of her clothes. At the time of our examination, twelve months after labor, she was experiencing slight itching and slight burning. Trichomonas vaginalis and gonococci were looked for but not found. The Wassermann reaction was negative. Cervical scrapings, in which inclusions could not be demonstrated, produced a typical infection in a baboon.

It is interesting to note that this woman's baby had conjunctivitis, with a discharge beginning on the ninth day after birth. No bacteria were found in two cultures. Some time later Staphylococcus aureus was observed, but no inclusion bodies. The disease lasted more than two months. The history is suggestive of inclusion blennorrhea. The scrapings may have been taken too late for inclusion bodies still to be demonstrable, for in the later stage of the disease there may be clinical symptoms but no inclusion bodies. If this was inclusion blennorrhea the mother either retained the bodies in her cervix until we examined her one year after the pregnancy or was reinfected in the interim.

CASE 2.—The second patient was a Negress. The scrapings from her cervix also produced a positive result on baboon inoculation, but the original cervical smear was negative for inclusion bodies. The history was as follows:

R. M. three years before had experienced pain in the lower part of the abdomen of sudden onset accompanied by a greenish yellow vaginal discharge and chills. There was tenderness in both lower quadrants and on movement of the uterus. Smears were negative for gonococci. The discharge continued and became white, watery and nonburning. Immediately before the examination in 1940 there was a return of the abdominal pain accompanied with a chill. On physical examination the patient was found to have thickening of the fornices and of the right tube and ovary. She had been married in 1929 and had separated from her husband in 1931. She had one child 7 years of age and one 5. The latter had had "runny" eyes at the age of six months. The patient had had sexual contact with other men since the separation from her husband but did not know that any of these men had urethritis.

CASE 3.—In the scrapings from the cervix in the third case there were both elementary bodies and inclusion bodies, and the baboon test gave positive results. Material curetted from the uterus revealed no

inclusion bodies. Smears from the urethra were also negative. The history was as follows:

G. S., a woman aged 20, had had a spotting white discharge for nine months prior to examination for the virus. She had no associated vulvitis or itching. Smears were negative for gonococci. She admitted frequent sexual intercourse in the past two years.

CASES 4 AND 5.—In these cases there were typical free elementary bodies in preparations of cervical scrapings but baboon inoculations gave negative results. The histories were as follows:

C. C., a white woman 48 years old, had had a yellow vaginal discharge for four to five years before the examination for the virus. In the past year it had increased in amount, occasionally running down her leg. There was no itching or odor. Menopausal symptoms had been present for the past year. She had been pregnant three times and had borne three children. The cervix was enlarged, firm, cystic and greatly inflamed; the uterus was retroverted; the adnexa were not felt.

A. H., a woman 38 years old, complained of dull pain in the right lower quadrant which had been present intermittently for the past twenty-two years. Lately she had had cystitis, due to hemolytic Staph. aureus. Two years before she had had salpingitis and a sterilization operation. A white spotting vaginal discharge was present at the time of examination.

In the series of 131 cases of vaginal discharge the virus was present in the cervix in 3.8 cases per hundred.

Of the 53 cases in which gonococci were identified, the virus was found in 5 by microscopic examination (fig. 5) but baboon inoculation gave positive results in only 3 of the 4 in which it was done. So far as could be determined there were no clinical signs which differentiated these cases from those in which gonococci alone were present. In all 5 cases there was gonorrheal urethritis, but in no case was the virus found in the urethra.

These results confirm our previous findings that the virus of inclusion conjunctivitis may be found not only in the cervices of mothers of babies with inclusion blennorrhea but also in the cervices of women with various gynecologic complaints.

In Urethral Scrapings from Men with Urethritis.—Through the cooperation of the Division of Social Diseases of the New York Department of Health [22] it was possible to study cases from the social disease clinic of fresh untreated urethritis. One hundred consecutive cases of acute anterior urethritis were studied by smear and by baboon inoculation. The virus of inclusion conjunctivitis was demonstrated by baboon

22. Dr. Michael Wishengrad, of the department of health, provided cases for this study.

inoculation in 8 of these 100 cases (table 8). In 6 of the 8 it was associated with a typical gonorrheal infection. In the 2 cases in which gonococci could not be demonstrated the urethritis was much milder, having a subacute onset and causing a relatively scanty discharge. In these cases the virus was seen in the form of elementary bodies only, there being insufficient epithelium for the demonstration of inclusion bodies. It was not possible to observe these cases through to healing.

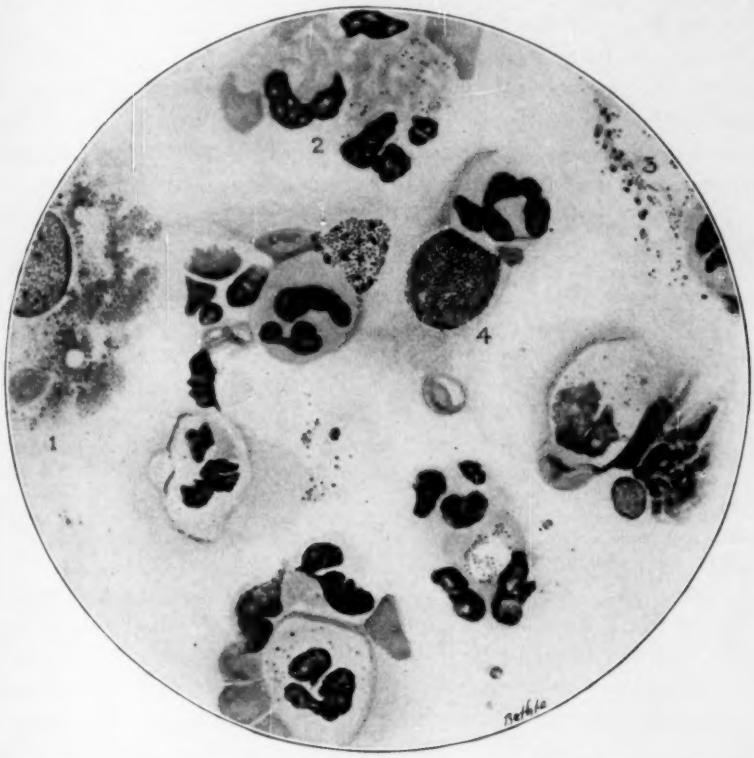

Fig. 5.—Drawing of inclusion bodies in cervical scrapings from a patient with acute cervicitis (Giemsa stain).

In addition to this series, a group of 7 selected cases of urethritis in which gonococci could not be demonstrated were studied. In all but 3 of these the inflammation was of longer duration than would be expected from the inclusion blennorrhea type of infection. The virus was found in only 1 case. This was the only case in the New York series which provided a clearcut example of the apparently pure inclusion virus urethritis of the type which occurred in the Iowa series and was cited in the previous report with W. L. Mengert.[10] In the Iowa case there was what is believed to be the characteristic picture of the infection in

the urethra, i. e. subacute onset, low grade infection, a series of mild exacerbations and healing without sequelae. In the series of 100 unselected New York cases the 2 cases in which gonococci were not found were apparently instances of the pure infection in that they showed no significant bacteria in smears and exhibited no clinical evidence of lymphogranuloma venereum. The infection was mild and had the subacute onset believed to be characteristic of inclusion infection, but the fact that the cases could not be followed throughout the clinical course makes unequivocal classification impossible.

From these findings it would appear that the virus of inclusion conjunctivitis occurs not infrequently in cases of urethritis, although considerably less often than the gonococcus. Moreover, the infection may actually be more common than these figures indicate, since it may be so benign that the patient fails to present himself for treatment, and

TABLE 8.—*Data on Urethritis and Prostatitis in Which Urethral Scrapings Were Examined for the Virus of Inclusion Conjunctivitis*

No. of Cases	Condition	Discharge	Results of Examination for the Virus	
			Smears	Baboon Inoculation
7	Gonococcic prostatitis	Moderate to great	Negative	Negative
2	Nongonococcic prostatitis	Slight	Negative	Negative
6	Acute nongonococcic urethritis	Slight to moderate	Negative	1, positive
1	Chronic nongonococcic urethritis	Slight	Negative	Negative
100	Urethritis at onset, unselected as to type	Slight to great	2, positive	6, positive *

* Of the 6 patients, 4 had gonococci and 2 were bacteria free.

it must be borne in mind that the methods of demonstrating the virus are less sensitive than the methods of demonstrating the gonococcus.

Two additional cases observed recently are of decided interest because of the association of urethritis with a stubborn purulent chronic conjunctivitis unrelated to the virus of inclusion conjunctivitis. In the first case the conjunctivitis was the papillary type and of several months' duration. In the second case a severe keratoconjunctivitis with marginal infiltrates of several weeks' duration was associated with chronic arthritis and urethritis. That none of the infections were caused by the virus of inclusion conjunctivitis was apparent from the absence of inclusions in both urethral and conjunctival material and from the failure of the infections to respond to sulfathiazole, which they would surely have done if the inclusion virus had been the cause. Nor were the conjunctival infections follicular in character, as would have been the case with inclusion conjunctivitis of equally long duration. No cause was determined for either the urethral or the conjunctival conditions. Unfortunately Frei tests could not be made, but there was no involvement of the inguinal glands

or other clinical suggestion of lymphogranuloma venereum in either instance, and the conjunctival infections were accompanied with none of the regional adenopathy characteristically associated with them in lymphogranuloma venereum.

In Cases of Vaginitis in Children.—As had been noted by ourselves [10] and by Braley,[20] the virus in women appears to localize in the epithelium just within the external os of the cervix. Many attempts to demonstrate the characteristic inclusion bodies in epithelium of the vagina have been unsuccessful, and it is our belief that the failure of the virus to affect this epithelium is due to its being a keratinized glycogen-containing type. The only type of cell in which inclusions have been demonstrated is that found in the conjunctiva, just within the external os of the cervix of the adult female, in the vagina of the young girl and in the urethra. In view of the apparent susceptibility of this particular cell type, it seemed logical to look for the virus in cases of vaginitis in children. In a study of 53 such cases Dr. Grace C. Hardy,[22a] working in our laboratory, found the virus by baboon inoculation and by microscopic study in 2. No other etiologic agent was found in these cases.

SIGNIFICANCE OF THE GENITOURINARY DISEASE

Although the existence of a genitourinary infection caused by this virus was deduced as early as 1910 by Lindner,[23] gynecologists and urologists have ignored the infection until recently. In a recent survey in *The British Journal of Venereal Diseases* L. W. Harrison and W. Worms [24] reviewed the literature on the relation of this and other viruses to nongonococcic urethritis and in particular to so-called Waelsch urethritis, a type characterized by its long incubation period (from five to sixteen days), the mildness and chronicity of its subjective symptoms and its almost complete resistance to local treatment. That the inclusion virus may be concerned in the causation of this condition is suggested by the observation on urethroscopic examination of sago-grain-like follicles resembling those observed on the conjunctiva in inclusion conjunctivitis. Furthermore, the condition has been found to respond to sulfanilamide and its derivatives, as would be expected of an infection caused by this virus. On the other hand, there is the observation of

22a. Hardy, G. C.: Vaginal Flora in Children, Am. J. Dis. Child. **62**:939 (Nov.) 1941.

23. Lindner, K.: Zur Aetiologie der gonokokkenfrein Urethritis, Wien. klin. Wchnschr. **23**:283, 1910.

24. Harrison, L. W., and Worms, W.: The Relation Between Some Forms of Non-Gonococcal Urethritis, Lymphogranuloma Inguinale, Trachoma, and Inclusion Blennorrhea, Brit. J. Ven. Dis. **15**:237, 1939.

Bezecny,[25] who found that urethral secretion from a patient with Waelsch urethritis acted like Frei antigen, a fact which would strongly indicate the presence of the virus of lymphogranuloma venereum.

In view of the fact that the virus of inclusion conjunctivitis has been demonstrated in cases of nongonococcic urethritis by a number of different investigators, including Lindner,[23] Fritsch, Hofstätter and Lindner,[26] Thygeson and Mengert [10] and ourselves, we believe that inclusion virus urethritis does exist as a clinical entity. Since the virus is known to induce follicular hypertrophy of the conjunctiva, it would seem reasonable to expect similar follicular formation to be characteristic of the urethritis, but any conclusion to this effect must await urethroscopic studies of the infection.

Although we have been unable to establish any relation between the virus and urethritis in the female, it must be mentioned that the virus inclusions were found by Halberstaedter and Prowazek [27] in urethral scrapings from mothers of babies with inclusion blennorrhea even though no symptoms were present.

There is as yet no proof that the virus in the cervix causes clinical signs or symptoms. The subclinical nature of the cervical infection could well be due to the smallness of the area of susceptible cervical epithelium involved. The amount of exudate produced by this area of transitional epithelium must necessarily be scanty. It is noteworthy that in the female baboon a clinically recognizable cervical inflammation results from inoculation with the virus.

As previously mentioned, there is a possibility that the virus may be a factor in unexplained postpartum fever, for the postpartum morbidity in our series of mothers whose babies had inclusion blennorrhea was more than twice the average for the Sloane Hospital for Women over the same period. There has been no postpartum mortality among the mothers of infected babies. A definite statement as to sequelae must await further studies, but we have little evidence to support Hamburger's hypothesis that the virus causes adhesive salpingitis and no evidence to support his claim that it causes vulvitis. The findings of Dr. Grace Hardy suggest that the virus may be an infrequent cause of vaginitis in children.

EPIDEMIOLOGY OF INCLUSION CONJUNCTIVITIS

In the Newborn.—The 38 cases of inclusion blennorrhea of the newborn in this study were in no way exceptional. Although in a few cases

25. Bezecny, R.: Gekreuzte Ueberempfindlichkeitsreaktion bei Lymphogranuloma inguinale und Urethritis Typus Waelsch, Med. Klin. **30**:121, 1934; cited by Harrison and Worms.[24]

26. Fritsch, H.; Hofstätter, A., and Lindner, K.: Experimentelle Studien zur Trachomfrage, Arch. f. Ophth. **76**:547, 1910.

27. Halberstaedter and von Prowazek.[9b]

the apparent onset of the conjunctivitis was delayed until after the mother's discharge from the hospital on the tenth day, there was no indication that extragenital infection occurred. The incubation period, measured from birth to the onset of symptoms, averaged from seven to eight days; the onset was recorded in no case before the fifth day and in only a few after the tenth day. In these the conjunctivitis was recognized only after the patient had left the hospital. The symptoms of

TABLE 9.—*Data on Inclusion Conjunctivitis (Follicular) in Adults*

No.	Name	Duration	Origin
1	D. L.	1 month before treatment; cleared with sulfanilamide	No history of swimming in pool; no one else in family infected
2	E. B.	1 week before treatment; cleared with azosulfamide	No history of swimming in pool; no one else in family infected
3	V. R.	3 weeks before treatment; cleared with sulfanilamide	Gynecologist; definite history of contamination during a delivery 7 days before; spanked a baby and got meconium in his eye
4	G. V.	4 weeks before treatment; cleared with sulfanilamide	No history of swimming in pool; no one else in family infected
5	M. D.	2 weeks before treatment; cleared with sulfanilamide	No history of swimming in pool; no one else in family infected; examination of babies' eyes gave negative results
6	G. G.	Sulfanilamide treatment immediately; cleared	Had been swimming in pool 7 days previous to onset
7	O. B.	1 month before treatment; cleared with sulfanilamide	No history of swimming in pool; no one else in family infected
8	R. T.	3 weeks before treatment; cleared with sulfanilamide	Bathed in swimming pool 1 week previous to onset
9	L.	3 weeks before treatment; cleared with sulfanilamide	Had been swimming in pool 1 week previous to onset; no one else in family infected
10	D.	2 weeks before treatment; cleared with 5% sulfathiazole ointment applied locally	Gynecologist; no direct history of contamination; no urethral discharge
11	D.	Treated immediately with 5% sulfathiazole ointment locally; rapid healing	Wife of preceding patient; conjunctivitis developed while she was treating husband's eye
12	M. E.	Treated immediately with 5% sulfathiazole ointment locally; rapid healing	Swam in city pool 1 week prior to onset

inclusion blennorrhea during the first day or two may be mild and easily overlooked, and it is our opinion that the incubation period is seldom if ever longer than ten days.

As far as can be determined, therefore, inclusion conjunctivitis in the newborn occurred in all the cases in this series as a birth canal infection.

In the Adult.—The 12 cases in which inclusion conjunctivitis was not contracted at birth (table 9), though a small group, represent the important epidemiologic possibilities that have been considered.

Swimming Pool Transfer.—There were 4 examples of inclusion conjunctivitis apparently contracted from a swimming pool. In each case the incubation period appeared to be exactly seven days. No history of

other cases in which the disease was traceable to these particular pools was obtainable, although there may very well have been some such cases.

There seems to be little doubt that chlorination and other methods of disinfecting pools have cut down the incidence of inclusion conjunctivitis contracted from swimming pools. In an effort to obtain data on this mode of transfer we questioned by letter the student health officers of fifty prominent universities and colleges throughout the country. Only one report was returned of experience with the disease in epidemic form; the epidemic had occurred a number of years ago, prior to use of chlorination. Except in two instances we received no history of the occurrence of the disease in sporadic form, although transient irritations of the eyes, probably chemical in origin, were reported as being not unusual.

In an effort to secure data on the survival of the virus in water, epithelial scrapings from a patient whose inclusion blennorrhea was recently acquired were suspended in tap water and kept at room temperature for intervals of six, eighteen, twenty-four, thirty and forty-eight hours, respectively, and the suspensions were injected into baboons. The six hour suspension produced a positive reaction; the others, negative reactions. From this result it is evident that the virus can survive in untreated water for a sufficient length of time to permit transfer from person to person. It seems highly probable that genitourinary discharges are the source of contamination rather than ocular exudates. As has been mentioned by Bahn,[28] the habit of urinating in pools is probably widespread.

Accidental Infection of Gynecologists and Obstetricians.—Thygeson and Mengert [10] described the accidental infection of a gynecologist who was performing a dilation and curettage when blood from a bleeder spurted into his right eye. In spite of irrigation of the eye followed by the use of mild protein silver, typical inclusion conjunctivitis without significant bacteria followed on the eighth day. The infection healed after running a course of about five months.

In the present series we have 2 additional instances of infection in a physician apparently traceable to contamination with genitourinary material:

CASE 1.—J. F. R., an intern in obstetrics at St. Vincent's Hospital for Women and Children, in Philadelphia, in December 1939 acquired conjunctivitis of the left eye which resisted the usual local treatment over a period of five weeks. When seen by us on Jan. 17, 1940 he had typical inclusion conjunctivitis of the follicular type; inclusion bodies were demonstrated and no significant bacteria were recoverable. The condition responded readily to sulfanilamide and healed without residual changes. There was a history of exposure to genitourinary material just one

28. Bahn, C.: Swimming Bath Conjunctivitis, New Orleans M. & S. J. **79**: 586, 1927.

week previous to the onset of the conjunctivitis, when during efforts to resuscitate a newborn infant material splashed into his face.

CASE 2.—A. H. D., a young gynecologist at Mount Sinai Hospital, New York, on April 10, 1941 had acute follicular conjunctivitis of the right eye without significant bacteria and with typical epithelial cell inclusions. There was no definite history of actual contamination with genital secretions, but the gynecologist stated that there had been opportunities for accidental transfer. Seven days after the onset of symptoms the physician's wife showed a similar conjunctivitis, presumably contracted while applying medication to her husband's eye. In both the infection healed rapidly with local therapy with sulfathiazole.

In an effort to determine the frequency of this type of infection among gynecologists and obstetricians, letters were sent to the heads of departments and to other prominent specialists in this field in all the medical schools of the country. Table 10 outlines the data received in seventy-four replies. It is of interest that there were references to 20 cases of gonorrheal ophthalmia accidentally contracted and to only

TABLE 10.—*Data from Questionnaires on Accidental Infection of Gynecologists and Obstetricians*

Number of Replies	Number of Cases of Gonorrheal Ophthalmia	Number of Cases of Nongonorrheal Conjunctivitis Not Resembling Inclusion Conjunctivitis	Number of Cases of Nongonorrheal Conjunctivitis in Which the History Was Like That of Inclusion Conjunctivitis
74	20	6	3

3 cases of conjunctivitis of long duration in which the history suggested inclusion conjunctivitis. One of these is of particular interest:

Dr. R. G. D., an obstetrician and gynecologist at the Lying-in Hospital, in New York, in October 1934 had acute conjunctivitis with edema of the lids and a profuse purulent discharge. Smears and cultures showed no significant bacteria, and scrapings examined in the hospital laboratory showed no inclusion bodies. He was in the hospital for nearly a month and left with the disease still active. The discharge continued throughout the winter, and there was an exacerbation in one eye in April 1935. The condition finally cleared after running a course of about six months. The physician was cared for by Dr. Bernard Samuels and Dr. M. L. Berliner, who have informed us that the clinical picture was that of an acute follicular conjunctivitis with swollen and tender preauricular nodes. It is our opinion that this infection was in all probability inclusion conjunctivitis, the negative results of examination for inclusion bodies being accounted for by the fact that a technician unfamiliar with inclusion bodies was the only one to examine the slides. The physician recalled that some vaginal secretions were thrown back into his eyes while he was experimenting with an apparatus designed to obtain secretion from the uterus without contamination from the cervix.

The other 2 cases of severe, prolonged nongonorrheal conjunctivitis may well have been instances of inclusion conjunctivitis, but the histories obtained were insufficient to warrant the drawing of conclusions.

It should be mentioned that in 1936 Marchesani [29] reported the development of follicular conjunctivitis with inclusions in the eye of a woman physician who was splashed with amniotic fluid.

Eye to Eye Transfer.—There have been few reports in the literature of the transfer of the infection from the eye of one person to the eye of another. Sattler [30] in 1881 described the case of a mother in whom trachoma developed as a result of infection from the conjunctival discharge of an infant. Because of the similarity in appearance of inclusion conjunctivitis and trachoma, it is likely that this was inclusion conjunctivitis associated with the infant disease. Lindner reported 2 cases, 1 of accidental infection of the eye of a mother from an infected child and the other of infection of a sister from a baby with the disease. Noguchi and Cohen,[31] James,[32] and Thygeson and Mengert [10] each described 1 case of the accidental infection of a mother from her baby. Julianelle, Harrison and Lange [33] reported the case of a nurse who was infected from a baby. In the present series there was only 1 instance of heterologous eye to eye transfer. This was the instance previously noted in which the wife of a gynecologist contracted the disease, probably while treating her husband's eye. Both infections remained unilateral.

While there was only 1 instance in this series of spread from the eye of one person to the eye of another, there were 8 instances of spread from eye to eye in the same person, all of them infants. Since the minimum incubation period of the disease is five days, only cases in which the second eye became involved at least five days after the first are considered. The reason that unilateral conjunctivitis in the adult rarely spreads to the second eye is no doubt the fact that in the adult the infection is less severe, that there is less secretion than in the infant and that the amount of virus, as judged by the number of inclusion bodies, is much less. Furthermore, the way in which babies squirm around facilitates spread from one eye to the other, whereas adults usually make a definite effort to protect the second eye.

Transfer by Tonometer.—While visiting the Massachusetts Eye and Ear Infirmary, in Boston, in 1935 one of us (P. T.) had the opportunity of seeing in a group of patients with glaucoma 9 patients with inclusion conjunctivitis in whom the infection had arisen after tonometric exam-

29. Marchesani, O.: Einschlussblennorrhöe (Paratrachom) der Erwachsenen, Ztschr. f. Augenh. **88**:164, 1936; cited by Harrison and Worms.[24]

30. Sattler, H.: Klin. Monatsbl. f. Augenh. **19**:18, 1881; cited by Harrison and Worms.[24]

31. Noguchi, H., and Cohen, M.: The Relation of the So-Called Trachoma Bodies to Conjunctival Affections, Arch. Ophth. **40**:1, 1911.

32. James, W. M.: Inclusion Blennorrhea, Am. J. Ophth. **13**:1084, 1930.

33. Julianelle, L. A.; Harrison, R. W., and Lange, A.: Studies on Inclusion Blennorrhea, Am. J. Ophth. **21**:1231, 1938.

ination. All these patients had the conjunctival changes, e. g. follicular hypertrophy most marked in the lower fornices, which are characteristic of inclusion conjunctivitis, and inclusions were found in the 3 cases in which scrapings were taken. Through Dr. T. L. Terry we were able to obtain the history of these patients, which is summarized in table 11.

It is not clear how the first patient, in whom the onset of symptoms occurred June 4, 1935, received his infection, although the probabilities are that transmission occurred by way of the tonometer from some person not known to have had the disease. It is also not certain that patient 1 was the source of infection for some or all of the succeeding patients, although it seems more than probable that he was. There can be no doubt, however, that the infections did arise by transfer of the virus by means of the tonometer, since infection from any other source was not recognized during this period and since the range of the incubation

TABLE 11.—*Transmission by Tonometer of Inclusion Conjunctivitis*

Number of Cases	Previous Diagnosis	Date Tonometer Was Used	Reported Date of Onset of Conjunctivitis	Duration
1	Glaucoma	5/21/35	6/ 4/35	Slight activity when last seen, 1/14/36
2	Glaucoma	7/ 9/35	7/23/35	Healed by 12/ 8/36
3	Glaucoma	7/ 2/35	7/26/35	Healed by 10/15/35
4	Glaucoma	7/30/35	8/12/35	Some activity 1/25/36
5	Glaucoma	8/ 6/35	8/17/35	Slight activity 2/18/36
6	Glaucoma	8/ 6/35	8/21/35	Some improvement 9/3/35
7	Glaucoma	8/13/35	8/20/35	Healed by 6/27/36
8	Immature cataract	8/16/35	8/30/35	Onset in one eye; bilateral 7 days later; healed by 12/8/36
9	Secondary glaucoma; uveitis	9/ 4/35	9/11/35	Still active 12/21/35

periods (excluding that of patient 3) was seven to fifteen days, which corresponds to the range for inclusion blennorrhea in infants provided due allowance is made for the fact that prodromal symptoms may appear for several days before the really acute phase begins. The rarity of inclusion conjunctivitis, moreover, precludes the possibility that the use by these 9 patients of the tonometer could be a coincidence. It is interesting that in 1 patient the infection was unilateral at onset but spread to the second eye seven days later.

In view of the known susceptibility of the virus of inclusion conjunctivitis to drying it may be assumed that not much time elapsed between tonometric readings.

Autotransfer of Genitourinary Material to the Eye.—From none of the adults with inclusion conjunctivitis in this series was it possible to obtain a history of concurrent genitourinary infection, but neither was it possible from any to obtain material from the genitourinary tract for microscopic examination or for baboon inoculation. During the period of this study, as mentioned previously, 2 patients had simultaneous

nonspecific urethritis and conjunctivitis, but in neither was it possible to demonstrate the virus of inclusion conjunctivitis. Autotransfer from the genitourinary tract to the eye must be extremely rare, since few mothers of babies with inclusion blennorrhea have been reported as having the ocular infection. One mother whom we have observed showed the conjunctivitis some ten days after the birth of her baby, and it is probable that the infection was contracted by way of fingers contaminated in wiping the baby's eyes. Furthermore, none of the patients in whom the virus was demonstrated in either the cervix or the urethra showed ocular infection. So far as we could ascertain, no fathers of babies with inclusion blennorrhea had ever had inclusion conjunctivitis.

In this connection a case described by Lindner [23] is of interest. One week after intercourse a man showed a nonspecific urethritis and nine weeks later a trachoma-like conjunctivitis with inclusions, presumably a transfer from the urethritis. Although Lindner expressed the opinion that the conjunctivitis was trachoma, it was very likely inclusion conjunctivitis, since at that time Lindner [34] made no distinction between the two diseases.

Heterotransfer of Genitourinary Material to the Eye.—In addition to the gynecologists and obstetricians whose eyes were accidentally infected by genitourinary secretions, there is one patient in this series, a Negro elevator operator, who gave a history of perverted sexual intercourse with a young Negro woman one week prior to the onset of his ocular infection. He stated that he might have contaminated his eyes at that time. He failed to show a nonspecific urethritis.

RELATIONSHIP OF INCLUSION CONJUNCTIVITIS TO TRACHOMA

The morphologic identity of the inclusions of trachoma and of inclusion conjunctivitis, together with the similarity of the clinical signs of the two diseases in their early stages in adult patients and the similarity of the experimental diseases produced in monkeys and baboons, have led to certain confusions and misconceptions. Lindner [34] formerly thought that inclusion blennorrhea was identical with trachoma and deduced that there was a trachoma sui generis of the genital tract in both male and female. Later he concluded that although the two diseases are not identical an intimate relationship exists between the viruses producing them. He postulated the theory that the original localization of trachoma was probably the genital tract, whence the virus was transferred to the eye. He suggested that for hundreds or thousands of years the disease had been transmitted from eye to eye and that, adapting itself

34. Lindner, K., in Berens, C.: The Eye and Its Diseases, Philadelphia, W. B. Saunders Co., 1936, p. 441.

to this new location, it had changed its characteristics and become more tenacious. He stated that trachoma and inclusion conjunctivitis have a relationship similar to that existing between variola and vaccinia.

In an effort to establish differences or similarities between the two viruses which would be significant in this connection, parallel studies of them were undertaken. Attempts to obtain relevant serologic data failed completely, as no antibodies could be demonstrated for either disease or be produced by the injection of virus-containing material. Morphologically the two viruses appeared to be identical, but a significant difference was seen to exist between the relative amounts of carbohydrate matrix to be found in their respective inclusions. The elementary body inclusions of trachoma were demonstrable by the iodine method, all or almost all of them staining deeply. Only a small percentage of the elementary body inclusions of inclusion conjunctivitis were found to have a stainable matrix, and the inclusions were therefore difficult to demonstrate by this method in spite of the fact that they were generally more numerous than those of trachoma.

In addition to differences in character between the experimental diseases produced in human beings by the two viruses, the severity and the duration of the two experimental diseases in baboons were found to be at variance. Experimental trachoma in the baboon has a milder onset, a longer duration (up to eighteen months, instead of two to three months) and markedly fewer inclusions than experimental inclusion conjunctivitis in the same animal.

Of some importance in this connection is the clinical course of the experimentally produced inclusion conjunctivitis of one of us (P. T.) reported in the initial paper on inclusion blennorrhea.[5] A graded collodion membrane filtrate from a baby with inclusion blennorrhea produced typical inclusion conjunctivitis of the follicular type which, although at no time was there secondary infection, failed to heal spontaneously in the usual six month period. It was believed that a possible disturbance in the physiology of the eye due to a previous dacryocystectomy might have interfered with the normal process of healing. The eye continued to show follicular hypertrophy over a period of years without corneal changes, but in March 1938 superficial keratitis, characterized by punctate epithelial lesions, infiltrates and extension of limbal vessels, developed. This condition resisted local treatment for several weeks but regressed dramatically with sulfanilamide therapy. The clinical appearance of the keratitis was that of trachoma; there was no secondary infection. The only possible interpretations of this infection are (1) that it was inclusion conjunctivitis with superimposed trachoma and (2) that it was inclusion conjunctivitis which evolved into trachoma. In support of the first possibility is the fact that during the period of the experimental infection there were repeated exposures to trachoma, which was

under intensive study at the time. The infection in the baby from whom the filtrate was prepared ran the course of typical inclusion blennorrhea.

Neither in this case nor in any case so far found in the literature is there any convincing evidence to prove that trachoma may arise from any source other than a trachomatous eye. It should be pointed out, however, that Braley [35] recently advanced evidence to show that the cervix of the female baboon can be infected with the virus of trachoma. It seems likely, therefore, that the human cervix would be susceptible to experimental infection, although there is no reason to believe at present that spontaneous trachomatous infection occurs.

COMMENT

It seems evident from the assembled data that the study of the epidemiology of inclusion conjunctivitis is primarily a study of the genitourinary disease. Unlike the related disease trachoma, in which, so far as is known, eye to eye transmission is the rule, inclusion conjunctivitis is only rarely transmitted from eye to eye. It is our belief that if the genitourinary disease could be eliminated the virus would die out. In this respect the disease resembles gonorrheal ophthalmia, which, except in Egypt and certain other parts of the Near East, spreads from eye to eye only under exceptional circumstances.

It is interesting to speculate on methods of prophylaxis. In view of the rapid cure of the ocular disease obtained with sulfanilamide, it would seem likely that the genitourinary disease would also be susceptible. If all male patients with urethritis could receive early and adequate treatment it would probably result in eventual elimination of the disease in both male and female. Experience with gonorrhea, however, has shown that such mass treatment cannot be realized as yet. In view of the success obtained in the local treatment of inclusion blennorrhea with sulfathiazole ointment, the possible prophylactic use of this drug should be considered. It would be of decided interest to test the prophylactic value of applying the ointment at birth and for perhaps the first two or three days thereafter.

It is not possible from the data presented in this report to answer the many questions which can be asked regarding the frequency, localization and clinical importance of the genitourinary disease. Certain facts, however, have become evident. We believe it can be stated with certainty that the virus of inclusion conjunctivitis is one of the causes of nongonococcic urethritis and that the localization of the virus in the

35. Braley, A. E.: Relation Between Virus of Trachoma and Inclusion Blennorrhea, Arch. Ophth. **22**:393 (Sept.) 1939.

female is in the cervix in the transitional epithelium just within the external os. It is also possible to state that the virus is commonly found in the genital tract in association with the gonococcus but that it may occur alone. We believe it can be stated definitely that the virus does not produce vulvitis, as claimed by Hamburger,[17] and that it seems doubtful whether it causes chronic salpingitis, as suggested by the same investigator. Our impression is that the disease produced by the virus in the female is in most instances subclinical, a probability strongly indicated by the case histories of mothers of babies with inclusion blennorrhea.

SUMMARY AND CONCLUSIONS

Epidemiologic data derived from the study of 50 cases of inclusion conjunctivitis in infants, children and adults are analyzed and lead to the conclusion that the reservoir of the virus is a mild genitourinary disease which is probably transmitted venereally and in which low grade nongonococcic urethritis is the lesion in the male and subclinical cervicitis, apparently limited to the region of transitional epithelium just within the external os, the lesion in the female. The association of this virus infection with gonorrhea is common, but the two conditions appear to be entirely independent.

In this series the most common means of transfer to the eye was birth canal infection of infants during delivery, which accounted for the infection in all the infants. Other means of transmission included transfer by way of swimming pools, accidental infection of gynecologists or obstetricians with genitourinary secretions and probably transfer of genitourinary material to the eye by perverted sexual intercourse.

Eye to eye transfer was rare except in infants, in whom infections beginning unilaterally not uncommonly spread to the other eye. Nine instances of ocular infection which was probably spread from eye to eye by means of a tonometer are cited.

The parallelism of the epidemiology of inclusion conjunctivitis with that of gonorrhea appears to be very close except that gonorrhea does not seem to be transferred via swimming pools.

Miss Marie Montalto gave technical assistance.

ABSTRACT OF DISCUSSION

DR. ALSON E. BRALEY, Detroit: The problem of the epidemiology of inclusion conjunctivitis has been complicated by several factors beyond the control of the ophthalmologist. One must have the cooperation of the pediatrician, the obstetrician, the urologist and the family physician in order to obtain accurate data regarding the source of an ocular infection. Also, while the clinical diagnosis of inclusion conjunctivitis seems relatively simple to the ophthalmologist, it is not uncommon for a clinician to fail to think of it. Unfortunately, many of the clinical diagnostic

laboratories have had difficulty finding inclusion bodies and reporting their presence in conjunctival scrapings even when the disease was suspected clinically.

It is a common belief among mothers that many infants have a discharge from the eyes that last for several weeks after the baby is brought home. This was called to my attention recently in a case of unilateral acute follicular conjunctivitis. Several inclusion bodies were found in conjunctival scrapings. The patient said that she had been taking care of her 4 week old granddaughter and that the infant had some discharge from the eyes but not much more than would be expected. On examination of the infant many inclusion bodies were found in conjunctival scrapings.

Many babies in whom a profuse discharge from the eyes develops are suspected of having gonorrheal conjunctivitis and are immediately given sulfanilamide or a derivative, with prompt cure, and no definite diagnosis is made.

During the past two years I have seen 23 persons with inclusion conjunctivitis: 18 infants, 2 children and 3 adults. At Herman Kiefer Hospital, Detroit, during a period of three months in which there were 495 deliveries the infection was found in 16 cases—an incidence of 3.2 cases per hundred deliveries. While this incidence does seem excessively high, it may indicate that inclusion conjunctivitis is much more common than is thought. In a private hospital in Detroit where it was not possible to obtain conjunctival scrapings from all babies on the ninth day there was an incidence of 0.1 case per hundred deliveries.

In the case mentioned in which the infection was undoubtedly transferred from the infant's eye to the eye of the grandmother, the infant's mother did not have the conjunctival disease. An examination of her cervix was not possible.

In another case infection occurred in a medical student fourteen days after he had left a gynecologic service.

Dr. Thygeson and Dr. Stone are to be congratulated on the fine material presented in this paper. They have added greatly to knowledge of the troublesome yet apparently innocuous disease.

DR. L. A. JULIANELLE, St. Louis: That inclusion conjunctivitis, or inclusion blennorrhea, as it was originally designated, is more properly a venereal than an ophthalmologic infection has been realized since the fact was pointed out by Lindner some thirty years ago. Confirmed from several different sources, the concept soon took form that the newborn infant acquired the conjunctival counterpart of the genital disease in transit through the uterine canal immediately before birth. This explained why several days elapsed before onset of the conjunctivitis. It was only a matter of time before it was demonstrated that inclusion bodies in every way similar to those of trachoma were present not only in the epithelial cells of the infected conjunctiva but in the genital epithelial cells of the mother and father, as indeed in cases of so-called nonspecific urethritis. Scrapings of epithelial tissue from all three sources, moreover, were found by several workers to transmit the ophthalmic infection to baboons and monkeys, even to the reproduction of inclusion bodies in the conjunctiva. While the usual route of dissemination reported was from uterus to conjunctiva, occasional cases

were reported both at that time and even later, of infection spreading spontaneously and directly from eye to eye in human beings. The disease in the adult eye, however, presented a somewhat different clinical picture, reproducing what was known as bath conjunctivitis.

Subsequent studies by various workers indicated that the genitourinary manifestation is a mild infection, usually of short duration with occasional exacerbations but most frequently masquerading as *infection inapparente,* to use Nicolle's description. It has consequently been difficult to estimate its frequency, since mere questioning of parents yielded little specific information. Except, therefore, for the obvious fact that for every infant born with inclusion conjunctivitis there must be at least one adult, and probably two, with the genital disease, there have been no tangible statistics on its general distribution. Even if one accepts for discussion the data available on inclusion conjunctivitis in the newborn, on which accurate and adequate figures are still needed, the ratio of occurrence is certainly under 1 per cent and is probably close to 0.5 per cent. These figures differ markedly from the more than 13 per cent reported by Credé for gonococcic conjunctivitis of the newborn before the adoption of prophylactic measures. It may well be that the venereal infection recognized abroad as Waelsch or millet seed urethritis, a review of which was recently published by Harrison and Worms, is the same condition as inclusion urethritis. The evidence marshaled by these authors includes the fact that the infection is a granular urethritis "suggestive of trachoma," the presence of inclusion bodies and, what should appeal to Dr. Thygeson, prompt response of the infection to sulfanilamide therapy.

The communication presented by Dr. Thygeson and Dr. Stone describes, I believe, the first attempt to quantitate the occurrence of inclusion urethritis in the male and of inclusion cervicitis in the female. Of the 183 women studied 10, or approximately 5 per cent, had demonstrable disease. Of the 107 men, on the other hand, 9, or almost 9 per cent, were infected. The infection, therefore, is roughly twice as frequent in the male as in the female, and among the conditions conjunctivitis runs a poor third, occurring approximately one twentieth as often as urethritis and one tenth as often as cervicitis. Because gonorrhea possesses several characteristics in common with inclusion urethritis it may be useful to make certain statistical comparisons between the two diseases. Thus, the frequency of gonorrhea varies, depending on the locality and on the size of the community; it is from 0.7 to 2 per cent for the total population in large cities and from 1 to 4 per cent in small cities, with an average rate close to 1 per cent and a frequency twice as great in males as in females. If, therefore, the cases selected for study by Dr. Thygeson and Dr. Stone represent an equable sampling, it would seem that the ratio of infection in the male to that in the female approaches the ratio for gonorrhea, i. e. 2: 1, but that the incidence of inclusion disease is ten times as high as the incidence of gonorrhea. This ratio is so surprising that if the low rate of conjunctivitis in the newborn is to be explained one must assume either that the sampling was inaccurate or that the disease is mild and transient.

As Dr. Thygeson and Dr. Stone bring out, there need be little reason for confusing lymphogranuloma venereum and inclusion urethritis. Too

much emphasis is being placed by various writers on the superficial resemblances of the so-called inclusions of the two conditions. With such vast differences in pathogenicity, in pathologic response, in susceptibility of different animals and, just as important, in the nature of the infectious agent, it seems a far cry indeed to relate the viruses because of the similar morphologic appearance of these tiny structures.

I shall be interested to know later of the prophylactic effect of sulfanilamide and its derivatives on inclusion conjunctivitis. I dare say a single treatment, as in the Credé method for gonococcic conjunctivitis, will not be sufficient.

I should like to congratulate Dr. Thygeson and Dr. Stone on the start they have made along an arduous approach to this disease. I shall look forward to their future studies, feeling assured in the meantime that they have added another interesting and important contribution to a subject too long dormant after the brilliant studies of their early predecessors.

Dr. James E. Lebensohn, Chicago: I recently had the opportunity of seeing in more or less epidemic form inclusion conjunctivitis in a camp in which there were several thousand people. The cases were in groups of 3 at four different periods, which would indicate that there is little infectivity to inclusion conjunctivitis, because so few in a possible thousand or more persons were affected, and also that the chlorine used in water is not entirely prophylactic. During the same period I saw 1 adult who had a severe infection from a privately operated pool.

It is probably worth while putting these cases of the infection in adults on record.

Dr. Phillips Thygeson, New York: Dr. Julianelle's point in regard to the so-called Waelsch urethritis is interesting and one which we have been considering. It seems likely that since the inclusion virus produces a follicular hypertrophy of the conjunctiva it may well induce a similar hypertrophy in the urethra.

I neglected to bring out several points in regard to the frequency of the disease. I believe that estimating the frequency from the number of babies with inclusion blennorrhea does give too low a figure, since it is well known that only one eye of a baby may be affected and since Howard has recently reported an instance in which the infection developed in only one of a pair of twins.

We believe, furthermore, that the methods of sampling to detect the virus are still crude and that later figures will undoubtedly show a higher incidence of the disease.

CHOROIDOSIS CENTRALIS SEROSA

DIAGNOSIS, PATHOLOGIC PHYSIOLOGY AND THERAPY

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UTICA, N. Y.

The fundus lesion to be discussed in this article was first described in 1898 by Asayma, who designated it retinitis centralis. In 1929 Horniker [1] suggested the term central angiospastic retinitis and summarized the clinical findings as follows: The symptoms include sudden and sometimes short obscurations of vision, which in women tend to occur at the climacteric, and frequently there is a history of asthma, claudication and angioneurotic attacks. The objective findings include small white spots in the retina in an area of edema, small hemorrhages occasionally, changes in the smallest blood vessels and subsequent pigmentation of the lesion, with prompt relief following the use of vasodilators.

Ophthalmologists disagree as to the origin of this lesion. Some believe that it is of retinal origin, while others believe that it originates in the choroid and that the retinal changes are secondary. I believe that angiospastic lesions can occur both in the retina and in the choroid and that it is possible to determine which are of retinal and which are of choroidal origin. This article will deal chiefly with those arising in the choroid.

RETINAL ORIGIN OF LESION

Among the ophthalmologists who favor a primary retinal origin are Horniker [1] Gifford and Marquardt,[2] who, in addition to reviewing the literature fully, suggested the term central angiospastic retinopathy; Cattaneo,[3] who suggested retinal capillarosis as a diagnosis; Candian,[4] who designated the lesion an angioneurotic macular degeneration; Bailliart, who preferred the diagnosis of retinal capillaritis, and Junius, who described the lesion as a juvenile exudative macular retinitis. Cattaneo [3] stated that the lesion may be macular, paramacular or disseminated, and

1. Horniker, E.: Arch. f. Ophth. **123**:286, 1929.

2. Gifford, S. R., and Marquardt, G.: Central Angiospastic Retinopathy, Arch. Ophth. **21**:211 (Feb.) 1939.

3. Cattaneo, D.: Ann. di ottal. e clin. ocul. **65**:721 (Oct.) 1937; abstracted, Arch. Ophth. **20**:515 (Sept.) 1938.

4. Candian, F. L.: Ann. di ottal. e clin. ocul. **66**:824 (Nov.) 1938; abstracted, Arch. Ophth. **22**:698 (Oct.) 1939.

he expressed the opinion that circinate retinitis, senile macular exudative retinitis and disciform degeneration of the macula are also due to retinal angiopathy.

CHOROIDAL ORIGIN OF LESION

In 1920 Masada attributed the lesion to a *subretinal* exudate, and in 1922 Oguchi stated that this exudate not only originates from the choriocapillaris but both lifts off the retina from the choroid and passes into the retina. Abe in 1929 ruled out paresis of accommodation as a cause of the transient hyperopia which occurs in some cases. In 1938 Riehm [5] designated the lesion choroiditis centralis serosa. The Japanese prefer "chorioretinitis centralis serosa."

Walsh and Sloan,[6] who reviewed this phase of the subject, stated that unilateral dimness of vision, the presence of a positive scotoma and micropsia are typical symptoms and that transitory hyperopia and elevation of the macular region up to 3 or 4 D. are the important objective findings. Yellowish spots are sometimes seen in the retina, and the ill defined macular changes are suggestive of early choroiditis. They mentioned that in 1 of their cases the scotoma for blue was larger than the scotoma for red. They offered the term idiopathic flat detachment of the macula for this lesion because they believed the edema to be subretinal.

Verhoeff and Grossman,[7] in discussing the pathogenesis of disciform degeneration of the macula, made several fundamentally important observations. Concerning 1 of their cases they stated that the new tissue seemed to result from the organization of blood and that "the possibility cannot be excluded that the blood was derived from the choriocapillaris by diapedesis." Of another case they said that there was ". . . a serous exudate occurring primarily beneath the pigment epithelium behind the macula and elevating the retina here in the form of a mound." In discussing serous retinitis they stated, "The cause of this disorder has never been determined, but the observations in case 3 suggest that it may be serous exudation from the choroid." Later they said, "The observations in our cases do not exclude the possibility of a localized vascular lesion."

After mentioning the simultaneous occurrence of circinate retinitis in about 16 per cent of cases of disciform degeneration of the macula, they mentioned that, since lack of oxygen may cause deposition of fat in the tissues, a disturbance in the retinal capillary system may cause

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5. Riehm: Klin. Monatsbl. f. Augenh. **100**:617, 1938.

6. Walsh, F. B., and Sloan, L. L.: Am. J. Ophth. **19**:195 (March) 1936.

7. Verhoeff, F. H., and Grossman, H. P.: Pathogenesis of Disciform Degeneration of Macula, Arch. Ophth. **18**:561 (Oct.) 1937.

circinate retinitis and retinal hemorrhages. They summed up the differing effects of vascular dysfunction in different tissues as follows: "Since the structure of the retina is entirely different from that of the choroid, similar vascular changes in them might well produce different effects, in the one hemorrhages and deposits of fat, and in the other transudation of serum or hemorrhage by diapedesis or rupture." Verhoeff [8] closed the discussion of their article as follows: "A typical lesion is due to organization of a hemorrhagic extravasation which is primarily beneath the pigment epithelium. In some cases the hemorrhage may be due to urticaria. I can even bring my favorite factor, allergy, into the question."

DIFFERENTIAL DIAGNOSIS

Many lesions which have been diagnosed as retinitis centralis, angiospastic retinitis or disciform degeneration of the macula are probably of choroidal origin.

Spasms of the smaller branches of the retinal arteries do occur, but *they are rarely central;* the perivascular edema is white rather than gray or bluish; there is but slight elevation of the edematous area; micropsia is not a symptom; the field defect is larger for a red test object than for a blue test object of the same size (chart 1), and *subsequent pigmentary changes are not characteristic of the healed lesion.*

If, however, the edema is *behind* the retina and analogous to an urticarial wheal, it is easy to interpret the symptoms and signs as due to a localized subretinal accumulation of fluid. A primary choroidal origin of the localized edema accounts for the micropsia, the central blurring of vision, the transient hyperopia, the elevation of the retina, the field changes in which the scotoma for blue is always as large as and is usually larger than the scotoma for red (when both are present) and the subsequent changes in pigmentation. It may be recalled that *both pigmentation and depigmentation are characteristic of choroidal lesions.*

The secondary retinal changes can be explained by the passage into the retina of edema fluid containing histamine-like substances which cause narrowing of the retinal arterioles and dilatation and tortuosity of the retinal venules. There may be some edema of the retina, and white or yellow spots may develop in the edematous retina. Actually the lesion under consideration differs only quantitatively from acute exudative choroiditis, in which complete atrophy of the nerve fibers passing over the lesion usually occurs.

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8. Verhoeff, F. H., in discussion on Verhoeff and Grossman,[7] Arch. Ophth. **19**:467 (March) 1938.

The Friedenwald ophthalmoscope and red-free light are not essential for the diagnosis of this subretinal lesion. In the 13 cases reported in the accompanying table, the diagnosis was made on the basis of a history of a central blurring of vision or of micropsia, by tangent screen scotometry at 1 meter and by both indirect and direct ophthalmoscopy with ordinary light. In a few instances scotometry was done *prior* to the examination of the fundus and it was possible to *predict* that a primary choroidal lesion would be found.

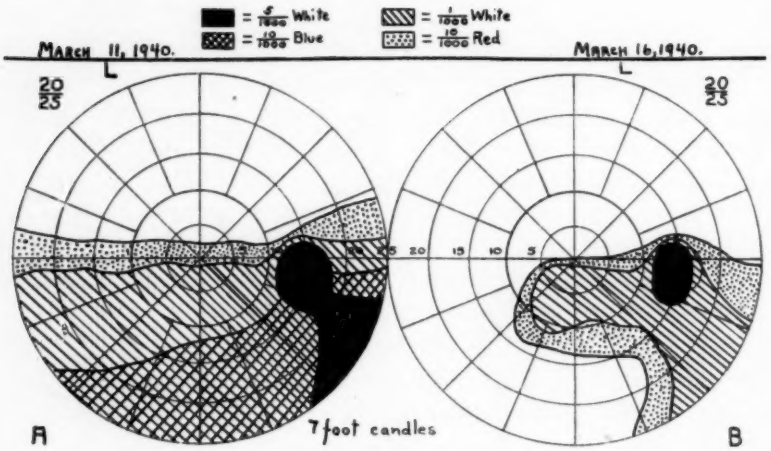

Chart 1.—Field defect of retinal angiopathy. The patient, a man of 70, had a partial closure of both the superior nasal-retinal artery and a small cilioretinal vessel which went to the retina above the macula. Symptoms had been present for four days before he was seen on March 11, 1940.

A, the field on March 11. In the lower temporal quadrant there was a defect, connected with the blindspot, for a 5/1,000 white stimulus. A 1/1,000 white stimulus was not perceived anywhere in the lower field. The defect for a 10/1,000 red stimulus was greater than the defect for a 1/1,000 white stimulus. This field was tested before the fundus was examined, and a diagnosis of closure of a retinal vessel was made on the basis of the results.

B, the field on March 16, after five intravenous injections of sodium nitrite (0.1 Gm.). At this time the superior nasal artery appeared normal but there was still edema of the retina around the cilioretinal artery. Most of the defect due to the occluded superior nasal artery had disappeared but there was still a defect for a 1/1,000 white stimulus corresponding to the closure of the cilioretinal artery. A 10/1,000 blue stimulus was perceived normally throughout the field, but the defect for a 10/1,000 red stimulus was slightly larger than that for a 1/1,000 white stimulus.

The field defect within the 15 circle in *B* is typical of isolated retinal angiopathy but not of choroidal angiopathy, in which the defect for blue is always as large as and is usually larger than the defect for a red test object of the same size (charts 2 to 6).

In younger patients the lesion seems to bear the same relation to acute exudative choroiditis that an urticarial wheal bears to erythema nodosum. The differences are of degree rather than of kind. Moreover, the differences between simple subretinal edema and disciform degeneration of the macula are due only to quantitative variations in the amount and the type of transudate from the choriocapillaris. Organic changes in the walls of the choroidal arteries and arterioles, the accompaniment of advancing age, probably account for the differences in the central subretinal lesions which occur in the different age groups.

Because the lesion is due to an increased permeability of the choriocapillaris, because it is primarily subretinal (as is shown by the impaired function of the rods and cones, as demonstrated by scotometry) and because it is of circulatory rather than of inflammatory origin, I think that the term choroidosis centralis serosa describes its location, origin and nature more precisely than previously suggested terms.

PATHOLOGIC PHYSIOLOGY

According to Ricker [9] many lesions are vascular in origin and due to increased capillary permeability. He differentiated three types: prestasis, or liquorstasis, in which plasma passes out into the surrounding tissues; peristasis, or leukostasis, in which white blood cells (chiefly lymphocytes) accumulate in the perivascular regions, and stasis, or rubrostasis, in which erythrocytes pass through the capillary walls.

Prestasis causes urticarial-like lesions such as occur in choroidosis centralis serosa and acute glaucoma (Kraupa; [10] Weekers and Barac [11]). Moreover, according to Kennedy [12] similar areas of localized edema in the white matter of the central nervous system account for the transient episodes of multiple sclerosis.

Peristasis results in lesions such as acute iritis and iridocyclitis, acute exudative choroiditis and acute retrobulbar neuritis.

Stasis causes purpuric lesions. Retinal hemorrhages and advanced disciform degeneration of the macula are examples of this type of capillary dysfunction in the eye.

Varying degrees of these three types of stasis occur clinically and account for quantitative variations in the rapidity of development, in the size and in the degree of many ocular lesions. Moreover, as men-

9. Ricker, G.: Sklerose und Hypertonie der innervierten Arterien, Berlin, Julius Springer, 1927; cited by Tooke, F. T., and Nicholls, J. V. V.: Am. J. Ophth. **21**:395 (April) 1938.

10. Kraupa, E.: Arch. f. Augenh. **109**:416, 1935; abstracted, Arch. Ophth. **16**:132 (July) 1936.

11. Weekers, L., and Barac, G.: Arch. d'opht. **1**:193 (March) 1937; abstracted, Arch. Ophth. **22**:135 (July) 1939.

12. Kennedy, F.: New York State J. Med. **36**:469 (April 1) 1936.

tioned by Verhoeff, the anatomy of the tissue in which these lesions of circulatory origin occur may modify the appearance and the development of the lesions.

Moon [13] has pointed out that when there occur focal lesions which show different degrees of altered capillary permeability, the microscopic picture is that of shock in miniature. He attributed most if not all of the pathologic changes to capillary anoxia. If there is capillary anoxia, as shown by the increased capillary permeability, tissue anoxia must occur, with a resulting depression in the function of the anoxic tissues.

There are as many causes of localized lesions due to increased capillary permeability as there are agents which can increase capillary permeability. Owing to the long domination of medicine by bacteriology, there is a widespread belief that because certain bacteria produce certain diseases with monotonous regularity similar lesions must always be due to the same etiologic agent. A new point of view based on the hypothesis that some focal abacterial lesions are physiologic in their early stages, i. e. due to overaction or underaction of homeostatic mechanisms which regulate the supply of oxygen-containing blood to the tissues, might eliminate some of the misconceptions regarding their origin, etiology and therapy which have been perpetuated because of the influence of the "dead hand" in medicine.

FACTORS CAUSING INCREASED CAPILLARY PERMEABILITY

Capillary permeability can be increased beyond physiologic limits by insufficient oxygen in the circulating blood, by histamine, by venoms, by certain drugs (especially the arsenicals and the iodides), by lack of cevitamic acid and by excessive arteriolar constriction.

Excessive arteriolar constriction can be caused by epinephrine, by nicotine, by histamine and by many other substances. According to Moon [13] and others this arteriolar spasm so limits the access of oxygen-containing blood to the capillaries that these become dilated and more permeable as a result of capillary anoxia. The tissues supplied by the capillaries in turn suffer from anoxia, and function is depressed.

Histamine can cause both arteriolar spasm and increased capillary permeability. The presence of histamine, histamine-colloid or histamine-like bodies in the circulating blood and their action on hypersensitive arterioles and capillaries can account for all lesions ordinarily attributed to cold, focal infection and allergy. The pathologic changes of allergy, anaphylaxis, histamine poisoning and epinephrine poisoning are all due to smooth muscle spasm and increased capillary permeability. All cause capillary anoxia and tissue anoxia. The manifestations of allergy and

13. Moon, V. H.: Shock and Related Capillary Phenomena, New York, Oxford University Press, 1938.

anaphylaxis are due not to "shock" tissues but to hypersensitive capillaries and smooth muscle, including the smooth muscle of the arterioles.

Other factors may also alter the reactions of arterioles and capillaries. Minz [14] has reported that thiamine acts by potentiating the action of acetylcholine, the vasodilator hormone of the body. Lack of nicotinic acid, which is a vasodilator according to Spies, Bean and Stone,[15] may contribute to the onset of these primarily vascular lesions. Moreover, thiamine, nicotinic acid and riboflavin are all said to play an important role in the oxidation of carbohydrate in the central nervous system. Reynolds [16] has reported that estrogen is cholinergic in that it apparently increases the acetylcholine content of rabbits' uteri. Hechter, Lev and Soskin [17] have also mentioned that estrogen has an acetylcholine-liberating action. Therefore, lack of the B vitamins and lack of estrogen may become clinically manifest as lesions which can be ascribed to circulatory insufficiency.

Finally, a temporary increase in the p_H of the blood, due either to the ingestion of alkali or to the "blowing off" of carbon dioxide (as in hyperpnea), can shift the dissociation curve of oxyhemoglobin to the left so that the oxygen is less readily liberated in the tissues. In the presence of any of the other causes of localized anoxia, this transient physiologic anoxemia could be of etiologic significance.

It must be obvious that there are many causes of localized tissue anoxia. The resulting lesions, which have been attributed to allergy, focal infection or tuberculosis, are due to changes in the blood vessels which are physiologic in nature but pathologic in degree. The arteriolar and capillary changes are the final common pathway whereby diverse causes produce similar lesions. Moon [13] has repeatedly stated that there is no necessity of searching for hypothetic toxins, since lesions which show the microscopic picture of shock are fundamentally due to anoxia.

It is readily understandable why lesions differ in the various age groups. In young adults the arterioles are elastic and can probably close almost completely, so that localized areas of acute necrosis often result, as in acute exudative choroiditis. In older persons organic changes in the arteriolar wall prevent complete arteriolar closure; the lesions develop more slowly and acute necroses are the exception. However, in lesions which progress slowly, connective tissue tends to fix and perpetuate early changes; so vasodilator therapy should be and is less effective than in young patients.

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14. Minz, B.: Presse méd. **46**:1406 (Sept. 2) 1938.

15. Spies, T. D.; Bean, W. B., and Stone, R. E.: Treatment of Subclinical and Classic Pellagra, J. A. M. A. **111**:584 (Aug. 13) 1938.

16. Reynolds, S. R. M.: Science **87**:537 (June 10) 1938.

17. Hechter, O.; Lev, M., and Soskin, S.: Endocrinology **26**:73 (Jan.) 1940.

Data on 13 Patients with Choroidosis Centralis Serosa

No. of Case	Age; Sex; Date First Seen	Symptoms; Duration	Vision	Fundus	Elevation of Lesion, D.	Scotoma (B, Blue; W, White)	Treatment *	Final Vision	Time of Improvement, Days: Vision	Field	Fundus	Details of Healing
1	20 ♀ 2/16/40	L. Micropsia and central blur; 25 days	20/20	Perimacular subretinal edema; retinal venules to macular region tortuous	0.5	2/1,000 B	4 SN	20/13—	8	5	5	Fundus normal
2	42 ♀ 12/29/39	R. Micropsia and central blur; 7 days	20/25	Macula red; perimacular region elevated; white spots in retina; retinal veins engorged	1	5/1,000 B	4 SN; ETN, 30 mg. daily for 2 weeks	20/13—	3	8	3	Residual white spots in retina
3	34 ♂ 6/2/39	R. Vision "bleary"; 3 days	20/20—	Grayish elevation of macula; no foveolar reflex; adjacent retinal vessels tortuous	1	10/1,000 B	6 SN	No change	—	5	5	Fundus normal
4	34 ♂ 4/24/39	L. "Fog" before eye; 21 days	20/30	Macular region hazy and granular; nearby small vessels tortuous	1	10/1,000 B	5 SN	20/20	4	7	11	During healing, white spots developed in retina; these later disappeared
5	37 ♂ 3/7/38	R. Micropsia and cloudy vision; 7 days	20/20	Macular region hazy; faint opacity of vitreous in front of macula	1	1/1,000 W 10/1,000 B	1 SN; ETN, 15 mg. twice a day for 7 days	No change	—	Less than 9 days		Patient symptom free after one treatment; did not return for 9 days
6	30 ♂ 1/16/39	L. Purplish spot before eye; 4 days	20/30	Temporal to macula, an oval granular elevated area; smaller retinal vessels tortuous	1	1/1,000 W 10/1,000 B	5 SN; ETN, 15 mg. twice a day for 13 days	20/20	2	18	18	Depigmentation and a few white spots in retina at site of lesion
7	45 ♂ 4/25/39	L. Gradual failure of vision; 7 months	20/50	Fine pigmentation of macula; white spots in retina; old atrophy of optic nerve; sheathing of inferior nasal vein	1-2	1/1,000 W 10/1,000 B	17 SN; ETN, 15 mg. daily	20/30	13	21	21	White spots in retina disappeared; granular appearance remained
8	55 ♂ 10/3/38	L. Vision poor; 2½ years	20/200	Macular region, a finely granular appearance; some sclerosis of retinal arterioles	1-2	1/1,000 W 10/1,000 B	13 SN	20/30	17	27	27	Macular region remained elevated 1 D.
9	60 ♀ 6/11/38	R. Blur before eye; 17 days	20/40—	Macula red; retina temporal to it, a finely granular appearance; retinal vessels to lesion tortuous	1-2	2/1,000 W	4 SN in 8 days	20/16—	40	—	19	Macular region remained elevated 0.5 D.; permanent scotoma for 2/1,000 blue
10	56 ♂ 11/7/38	R. and L. Progressive loss of vision; 4-5 years	R 20/200 L 20/200	Macular regions pale and granular; disciform elevation; optic nerves pale	R 2.5 L 3	2/1,000 W 10/1,000 B	23 SN in 10 weeks	R 20/50— L 20/70—	77	77	77	Macular region remained elevated 1 D.; scotomas decreased in size and density
11	48 ♀ 11/14/38	L. Sudden loss of sight; micropsia; 10 days	20/100	Disciform gray elevation of macular region; overlying vessels tortuous; two small hemorrhages on optic nerve	2	5/1,000 W	9 SN in 16 days; then ETN, 15 mg. twice a day	20/30	16	—	56	As lesion subsided, white spots appeared in retina; macula flat 1/11/39
12	61 ♂ 1/20/35	L. Central blur; 4-5 months	20/30—	Disciform bluish elevation of macular region about 4 mm. in diameter; marked arteriosclerosis of retinal arteries	2	2/1,000 W 10/1,000 B	6 SN	20/20—	5	5	Little change	Improvement maintained for 1 month; then hemorrhage into lesion reduced vision to 12/200, with typical fundus changes of Kuhnt-Junius disease
13	65 ♀ 3/26/38	R. Failing vision; several months	20/100	Bluish gray disciform elevation at posterior pole of eye; retina granular; overlying vessels tortuous	3	Blue	5 SN; then ETN, 30 mg. twice a day	20/50—	13	—	Little change	Improvement maintained for 2½ months, after which patient disappeared from clinic

* SN indicates 100 mg. of sodium nitrite given intravenously. All injections were given daily unless stated otherwise. ETN indicates erythrityl tetranitrate. This was given by mouth.

A normal supply of *available* oxygen is essential for normal capillary and tissue function. Most of the lesions due to localized anoxia occur in patients who do not have anoxemia. Therefore, the primary therapeutic requisite is to make oxygen-containing blood available to the capillaries and tissues. Arteriolar spasm may be assumed to be present in these patients (1) because of the signs or symptoms of vasospasm in other parts of the body and (2) because of the favorable response of the patients to vasodilators. Therefore, therapy directed toward the relief of arteriolar spasm should be the first consideration of the physician. With dilatation of the arterioles, oxyhemoglobin reaches the capillaries, oxygen is liberated, histamine or histamine-like bodies (if present) are oxidized, capillary permeability is decreased, the transudate is absorbed, the lesion regresses, tissue anoxia is relieved and function improves if the tissue anoxia has not lasted too long.

COMMENT ON CASES

In the accompanying table I have recorded the important facts concerning 13 patients who had a localized central subretinal accumulation of fluid. The diagnosis of the choroidal origin of the lesions is based on the presence of a scotoma only for blue or larger for a blue than for a white and for a red test object. These findings indicate a primary interference with the nutrition of the rods and cones. Typical fields are represented in charts 2 to 6. In all the charts which accompany this article the fields were plotted on the Thomasson[18] tangent screen according to the sensible principles outlined by Thomasson in 1926.

The cases have been listed according to the density of the scotoma and the extent of the fundus changes. The density of the scotoma is probably a better measure of the extent and the severity of the lesion than is the depression of visual acuity. In cases 1 to 4 only a scotoma for blue could be demonstrated. In cases 5 to 8 there was also a scotoma for a 1/1,000 white stimulus but not for larger white test objects. In cases 9 to 12 a scotoma could be elicited with a 2/1,000 or a 5/1,000 white stimulus. In case 13, in which the patient was uncooperative, a scotoma for white could not be plotted, but since the vision was 20/100 one must have been present.

Cases 1 to 6, in which the condition could have been diagnosed as "serous retinitis," are actually cases of acute choroidosis centralis serosa. Cases 7, 8 and 10 can be regarded as cases of chronic choroidosis centralis serosa because the condition had existed for from seven months to four years. Cases 11 to 13 fall into the group of cases in which the lesion is known as disciform degeneration of the macula, and case 10 probably belongs in this group.

18. Thomasson, A. H.: Simplified Tangent Screen with Suggestions on Field Taking, Arch. Ophth. **55**:545, 1926.

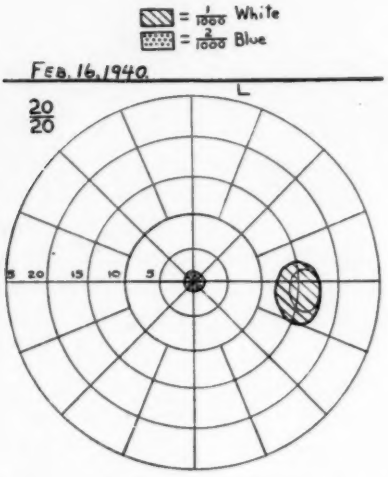

Chart 2.—The field of patient 1, a girl of 20. Despite the fact that the vision was 20/20 she complained of a central blur and of micropsia. A central scotoma was present for a 2/1,000 blue but not for 2/1,000 red stimulus. After five days the scotoma could not be elicited. After eight days the vision was 20/13—.

Chart 3.—The field of patient 4, a man of 34. A central scotoma was present for a 10/1,000 blue but not for a 10/1,000 red or a 1/1,000 white stimulus. On May 1, 1939 the vision was 20/20. No definite scotoma was present, but a 3/1,000 blue stimulus appeared bluish green at the fixation point.

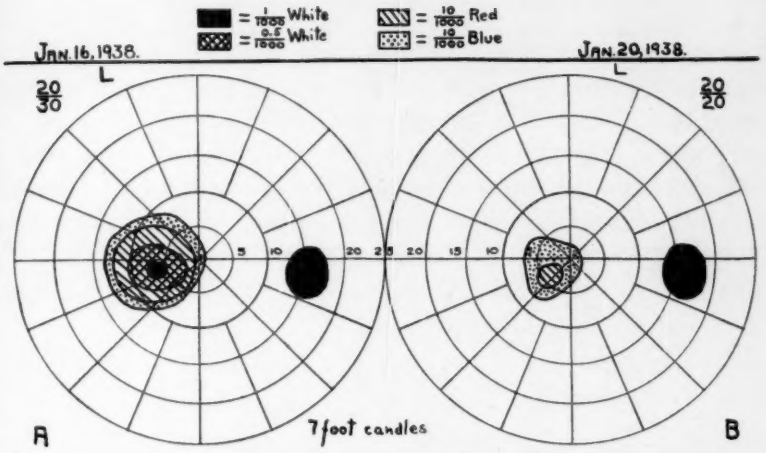

Chart 4.—The field of patient 6, a man of 30. *A*, the field on Jan. 16, 1938. There was a paracentral scotoma for a 1/1,000 and a 0.5/1,000 white stimulus, for a 10/1,000 red stimulus and for a 10/1,000 blue stimulus. The defect for blue was greater than the defect for red.

B, the field on January 20, after treatment. A scotoma only for colors was present. This defect was larger for blue than for red. The vision had improved to 20/20.

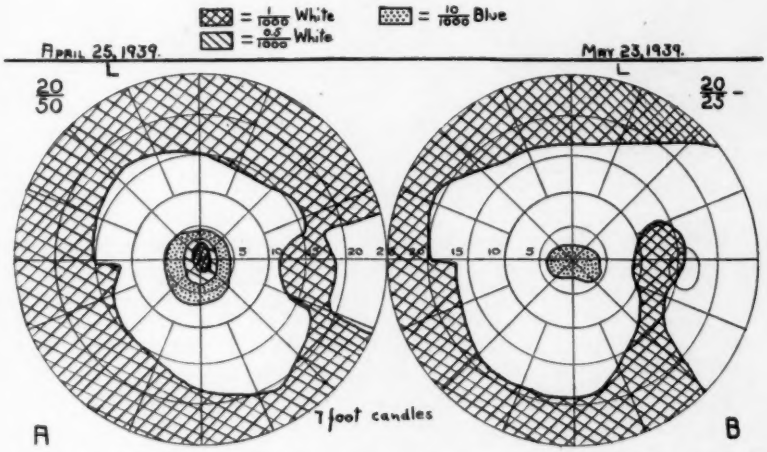

Chart 5.—The field of the left eye of patient 7, a man of 45. The peripheral defect connected with the blindspot was present on May 8, 1938, at which time the vision was 20/30. This defect was due to acute retrobulbar neuritis which had occurred in 1908. The optic nerve was white, and the patient could not distinguish red or green.

A, the field on April 25, 1939. A central blur had been present for seven months. The central scotoma was due to a new subretinal lesion at the macula, which was elevated about 1.5 D.

B, the field on May 23, after therapy. The scotoma for white had disappeared, but there was still a scotoma for a 10/1,000 blue stimulus. The vision had improved to 20/25—, which was better than could be obtained in 1938. The peripheral defect had also decreased slightly.

There is a definite increase in the extent of the objective findings (changes in fundus and field and lowered visual acuity) from case 1 to case 13. The patients' ages correspond roughly with this arbitrary arrangement. All the lesions were due to subretinal edema, but the rapidity of onset, elevation of the lesion and decrease in visual acuity varied from case to case because of quantitative variations in the extent and the degree of increased permeability of the choriocapillaris. In young patients such lesions develop rapidly and also disappear quickly with treatment. In older patients the onset is more insidious and with treatment improvement is slow and often incomplete. A likely reason for these differences has been mentioned.

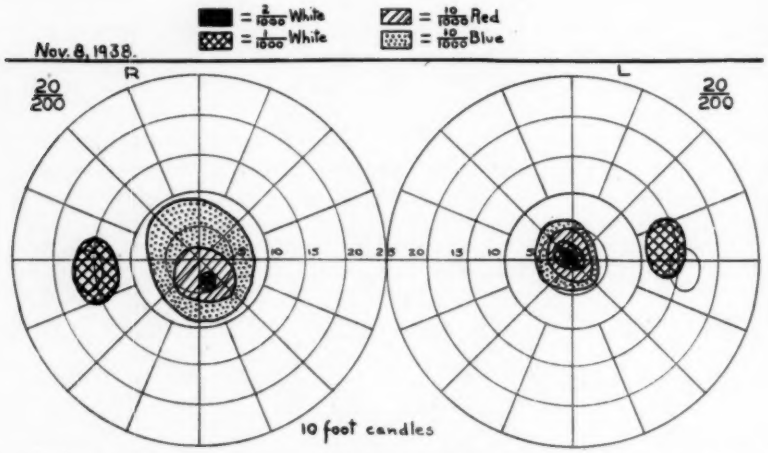

Chart 6.—The fields on Nov. 8, 1938 of patient 10, a man of 56. This patient had complained of progressive loss of sight for four or five years. The lesion was probably a mild form of disciform degeneration of the macula. The macular regions were elevated 2.5 and 3 D. The scotomas for blue were definitely larger than the scotomas for red. With treatment the vision had improved to 20/70 and 20/100 by Jan. 6, 1939. A small scotoma for white and a larger one for blue were still present in each eye at this time. On February 3 the vision was 20/50 in the right eye and 20/70 in the left eye. The macular regions were elevated about 1 D. With a +4.0 D. sph. reading addition the patient could read Jaeger test type 5 at 12 inches (30 cm.).

SYMPTOMS AND SIGNS

A central blurring of vision is the usual presenting symptom. A vision of 20/20 does not rule out a lesion. Test charts with which visual acuities of 20/16, 20/13 and 20/10 can be measured should be used.

Micropsia is a symptom only when there is little or no gross reduction of visual acuity or when the lesion is not exactly central. Four

patients (1, 2, 5 and 11) complained of micropsia, and the vision of the first three of these was 20/20 or 20/25. The vision of patient 11 was 20/100, the micropsia was slight and the lesion was not exactly central.

Transitory hyperopia is usually demonstrable only if the visual acuity is nearly normal. There was a transitory hyperopia of 0.25 D. in case 1, of 0.5 D. in cases 2, 4, 8 and 11 and of 1 D. in case 5. In cases 1, 2, 4 and 5 the vision was 20/30 or better; in case 8 it was 20/200 and in case 11 it was 20/100. Theoretically all patients showing an elevation of the macula should also have had transitory hyperopia, but a central scotoma for white probably prevented its demonstration in many instances. All the patients who complained of micropsia had transitory hyperopia.

The elevation of the lesions varied from 0.5 to 3 D. and corresponded approximately to the density of the scotoma. In cases 1 to 6 the visual acuity was depressed so slightly and the fundus changes were so insignificant that without the scotometric findings the correct diagnosis could easily have been overlooked.

TREATMENT

Treatment consisted of intravenous injections of sodium nitrite [19] (0.1 Gm.) in all cases. Seven patients also took erythrityl tetranitrate by mouth. Patient 9 received potassium iodide by mouth after some improvement had resulted from vasodilator therapy. Horniker,[1] Bailliart and Gifford and Marquardt [2] and others have previously mentioned the value of antispasmodic therapy in similar cases.

RESULTS OF THERAPY

Patients 1 to 6 recovered normal vision in from two to eight days. The scotomas disappeared in from five to eighteen days, and the fundus lesions subsided in from three to eighteen days. The results in the other patients were in general good, as shown in the accompanying table.

The 3 patients with disciform degeneration of the macula (patients 11 to 13) and the patient with borderline involvement (patient 10) all showed some improvement with antispasmodic therapy. To the best of my knowledge no other articles dealing with this lesion have concerned themselves with therapy. Patient 12 showed only temporary improvement, the typical late lesion of disciform degeneration of the macula developing later because of sudden extravasation of blood into the lesion. His case supports Verhoeff's statement that "the hemorrhage may be due to urticaria." The original lesion corresponded to an urticarial wheal; the relapse was due to an influx of erythrocytes by diapedesis rather than by rhexis into the area of edema.

19. E. Tosse and Co. supplied ampules of sodium nitrite for the treatment of several of the patients reported on.

EVIDENCES OF OTHER VASCULAR LESIONS

In patient 1 Bell's palsy on the left developed coincidentally with the ocular lesion. Patient 3 had previously had two attacks of acute retrobulbar neuritis. Both attacks were aborted with vasodilator therapy.

Patient 7 had had bilateral retrobulbar neuritis thirty years earlier, with resulting atrophy of the optic nerve and peripheral field defects. Prior to the attack of choroidosis centralis serosa the vision was 20/200 in the right and 20/30 in the left eye.

Patient 9 had had attacks of urticaria. The blood pressure was 108 systolic and 68 diastolic.

Patient 11 had lost useful vision in the right eye twelve years earlier after acute exudative choroiditis of the macular region.

Patient 12 had generalized arteriosclerosis and myocardial degeneration. The blood pressure was 142 systolic and 90 diastolic. The vision of the right eye had been poor for two or three years; the fundus showed typical advanced disciform degeneration of the macula and circinate retinitis.

ETIOLOGY

No single etiologic agent can account for the lesion in all these patients. The condition of patient 1 seemed to be a pure example of hypersensitivity to cold and therefore attributable to histamine. This patient had walked 1 mile (1.6 kilometers) to work before 7 a. m. on Jan. 22, 1940, at which time the temperature was 28 F. About 8 a. m. there occurred on the left a blurring of vision accompanied by paralysis of the left side of the face. Both lesions improved with vasodilator therapy.[20] In patients 2, 4, 5, 6 and 11 there seemed to be more than a casual relationship between exposure to cold and the onset of the ocular lesion.

Patient 2 may have represented an example of intraocular iodism, because she had received an intravenous injection of sodium iodide and sodium salicylate for rheumatism fourteen hours before the onset of blurring of the vision. The macula was red, the macular region was elevated 1 D. and there were several white spots in the elevated retina.

Patients 3 and 10 were heavy smokers, and the lesion of patient 4 might have been due to allergy following a head cold.

Patient 11 was a nervous, tense, "highstrung" woman. Excessive amounts of epinephrine in the circulating blood might have been of etiologic significance in her case.

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20. This is the fourth patient with Bell's palsy who has been treated with vasodilator therapy. The times required for improvement have been five, seven and eleven (2 patients) days.

Patient 12 had marked arteriosclerosis. Patients 9 and 13 might also be included among arteriosclerotic patients.

Meteorologic factors must also be considered. Petersen [21] reviewed case histories which "make evident the very simple relationship that exists between the precipitation of acute vascular episodes in the eye and the meteorological environment in which the patient exists." These acute vascular episodes include retinal hemorrhage, acute glaucoma, spasm of the retinal arteries, optic neuritis, chorioretinitis juxtapapillaris, episcleritis and idiopathic flat detachment of the macula (or choroidosis centralis serosa). Elsewhere in his monumental work he stated that the occurrence of iritis, Bell's palsy, urticaria and hypersensitivity to drugs is often related to meteorologic phenomena. According to Petersen meteorologic alterations occasion pressor episodes which may be generalized or localized to an organ or to part of an organ. These pressor episodes interfere with the supply of blood to the tissues, and anoxia results.

Prior to reading Petersen's contributions I had arrived at the same conclusion. It is my opinion that in some persons sudden changes in the external environment must be considered an important factor in any study of the causation of acute ocular disease. Petersen has discussed the whole subject so thoroughly and so well that anything I might add would be superfluous.

CONCLUSIONS

The term choroidosis centralis serosa seems to be appropriate for lesions at or near the macula which are due to localized subretinal edema.

A central blurring of vision is the usual presenting symptom. Micropsia and transitory hyperopia are likely to occur in patients who have only a slight depression of central visual acuity.

An elevation of the retina of from 0.5 to 3 or more D. and the presence of a scotoma only for the blue or larger for blue than for white and for red test objects are the important objective findings.[22]

Disciform degeneration of the macula differs only in degree from the mild lesions of choroidosis seen in young adults.

The retinal changes sometimes found in cases of choroidosis centralis serosa are the most obvious but the least important of the ophthalmoscopic findings. The retinal changes are probably due to the passage

21. Petersen, W. F.: The Patient and the Weather: Surgical Problems, Ann Arbor, Mich., Edwards Bros., Inc., 1938, vol. 4, pt. 3, pp. 557-590.

22. The colored test charts described by S. Engel (Colored Charts as Supplementary Test for Macular Vision, Arch. Ophth. **24**:910 [Nov.] 1940) should be of value in the diagnosis of this lesion.

of a histamine-like substance from the area of subretinal edema into the retina. This theory agrees essentially with Oguchi's interpretation of these changes.

These primary choroidal lesions should be differentiated from the lesions of central angiospastic retinopathy. Although the etiologic factors and the therapy are the same for both types of lesions, in my opinion choroidal angiopathy has a better prognosis than retinal angiopathy because the rod and cone cells seem able to withstand anoxia for a relatively longer time than the retinal ganglion cells.

All substances are possible etiologic agents which in virtue of their presence (histamine, epinephrine, nicotine, etc.) or their absence (acetylcholine, cevitamic acid, some factors of the vitamin B complex and possibly estrogen) can cause either arteriolar spasm or increased capillary permeability or both. The immediate result is tissue anoxia. *These vascular changes and the resulting tissue anoxia are the final common pathway whereby a number of apparently unrelated etiologic agents can produce the same pathologic lesion.* Lesions differ quantitatively rather than qualitatively and represent varying degrees of Ricker's stages of prestasis, peristasis and stasis.

Treatment with vasodilators has a sound physiologic basis. The chief function of this type of therapy is to increase the supply of oxygen-containing blood to the anoxic capillaries and tissues. If there are vitamin or other deficiencies, patent vascular channels enhance the opportunity for the needed factors to reach the morbid tissues.

HEREDITARY GLAUCOMA IN A PEDIGREE OF THREE GENERATIONS

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William H. Stokes [1] in the November 1940 issue of the ARCHIVES OF OPHTHALMOLOGY presented a pedigree of five generations with hereditary glaucoma. In addition he was able to find in the literature 27 pedigrees with hereditary glaucoma. The literature on the subject was so thoroughly covered in his report that it may be proper for us to omit many of the details. He has sent us the history of another family, reported by Paulo Cezar Pimentel [2] at the third Brazilian Congress of Ophthalmology in 1939. In this family, traced through five generations, 4 couples were cousins and 4 persons had hydrophthalmos, 3 had chronic glaucoma and 8 had myopia.

Certain features peculiar to hereditary glaucoma have been noted by investigators who have reported on this subject, and these workers have been fairly well agreed on the uniformity of the findings, although a few of the characteristics found in some pedigrees have not been found in others. Courtney and Hill,[3] Plocher,[4] Sattler,[5] Shumway [6] and others have classified hereditary glaucoma as belonging to the juvenile type. However, Anderson [7] found no absolute distinction between juvenile glaucoma and either congenital glaucoma (hydrophthalmia) or senile glaucoma. Elliot [8] similarly distinguished among congenital, juvenile

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1. Stokes, W. H.: Hereditary Primary Glaucoma: A Pedigree with Five Generations, Arch. Ophth. **24**:885-909 (Nov.) 1940.

2. Pimentel, P. C.: Consanguinity and Morbid Heredity, read before the Third Brazilian Congress of Ophthalmology, July 1939, unpublished data.

3. Courtney, R. H., and Hill, E.: Hereditary Juvenile Glaucoma Simplex, Tr. Sect. Ophth., A. M. A., 1931, pp. 47-68.

4. Plocher, R.: Beitrag zum juvenilen familiären Glaukom, Klin. Monatsbl. f. Augenh. **60**:592-619, 1918.

5. Sattler, R.: Juvenile Glaucoma, Tr. Am. Ophth. Soc. **10**:519-521, 1905.

6. Shumway, E., in discussion on Courtney and Hill.[3]

7. Anderson, J. R.: Hydrophthalmia or Congenital Glaucoma, London, Cambridge University Press, 1939.

8. Elliot, R. H.: Glaucoma, New York, Paul B. Hoeber, 1918, p. 317.

and senile glaucoma only according to the age group in which they appear. Keerl [9] in a study of juvenile glaucoma found heredity a factor in 18 per cent of his cases.

AVERAGE AGE OF ONSET

Bell [10] in 1932 stated the average age of onset of hereditary glaucoma to be twenty years earlier than the age of onset of glaucoma in her general series of glaucomatous patients. The average age of onset which has been reported in different pedigrees varies from 16 years to the late 60's. Stokes [1] found that females were affected a little earlier than males; this is also true of patients with nonhereditary simple glaucoma. It appears from the literature that the age of onset varies with the different families reported on. In Haag's [11] series of 67 the ages varied from 6 to 35.

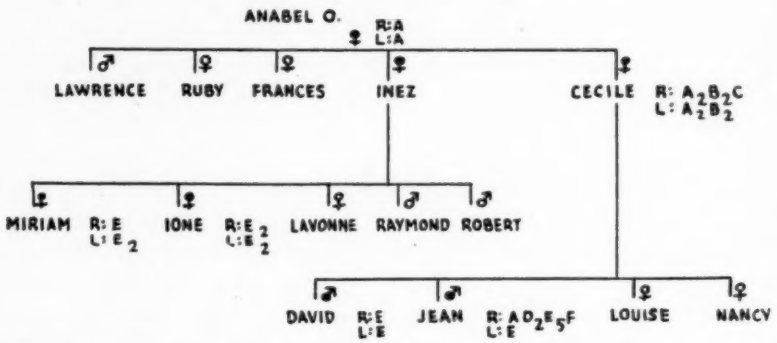

Chart 1.—Pedigree of family with glaucoma in three generations. Operations: *A*, iridectomy; *B*, paracentesis; *C*, sclerotomy; *D*, cyclodialysis; *E*, goniotomy; *F*, iridencleisis.

Löhlein [12] found juvenile glaucoma in the highest percentage of cases occurring at 15 to 20 years; 30 years was the limit at which juvenile glaucoma occurred. In the pedigree we are reporting the age of onset varied from 7 to 15 years, the average being 11.6 years.

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9. Keerl, M.: Das Glaukom der Jugendlichen, Inaug. Dissert., Leipzig, Emil Lehmann, 1920.

10. Bell, J.: On Some Hereditary Structural Anomalies of the Eye and on the Inheritance of Glaucoma, in Bell, J.: The Treasury of Human Inheritance, London, Cambridge University Press, 1932, vol. 27, p. 448.

11. Haag, C.: Das Glaukom der Jugendlichen, Klin. Monatsbl. f. Augenh. **54**:133-167, 1915.

12. Löhlein, W.: Das Glaukom der Jugendlichen, Arch. f. Ophth. **85**:393-488, 1913.

TENDENCY TO ANTICIPATION

Anticipation is the term given to the tendency for the condition to appear at an earlier age in succeeding generations. Von Graefe [13] in 1869 pointed out the tendency to anticipation, referring to a mother and daughter attacked in the same year although there was a difference of twenty-six years in their ages. Plocher,[4] Nettleship [14] and Calhoun [15] noted it in their family histories. In Courtney and Hill's [3] family no tendency to anticipation was noted. Bell [10] concluded that children tend to become affected about ten years earlier than their parents. In Stokes's [1] family no definite tendency to anticipation could be proved; the same can be said of our family.

The possibility must be kept in mind that members of a succeeding generation may be seen at a younger age than their parents and that earlier diagnoses can therefore be made (Stokes [1]).

SEX INCIDENCE

Löhlein [12] in a report on 92 glaucomatous patients found a slight preponderance of males. Of the 210 patients with glaucoma in the 27 pedigrees reviewed by Stokes,[1] 106 were males and 104 were females. In Stokes's pedigree there were 21 affected members in five generations, 12 males and 9 females. Stokes, therefore, found no marked distinction in the sex incidence. In cases of hydrophthalmia Anderson [7] reported a marked preponderance of males. In the pedigree we are presenting 5 females and 2 males were affected.

SEX TRANSMISSION

Stokes [1] expressed the belief that the two parents are equally potent in transmitting the disease and that the parent transmitting it is usually affected. Our genealogic tree is too short for conclusions to be drawn on this matter.

SIZE OF CORNEA

The normal corneal diameter at birth is 10 mm. (Wolff [16]), the period of greatest growth occurring during the first year of life, when the measurement may reach 11.4 mm. Priestly Smith [17] in his measure-

13. von Graefe, A.: Beiträge zur Pathologie und Therapie des Glaukoms, Arch. f. Ophth. (pt. 3) **15**:108-252, 1869.

14. Nettleship, E.: Some Hereditary Diseases of the Eye, Ophthalmoscope **4**:493-549, 1906.

15. Calhoun, F. P.: Hereditary Glaucoma (Simplex), Tr. Sect. Ophth., A. M. A., 1914, pp. 101-121.

16 Wolff, E.: The Anatomy of the Eye and Orbit, Philadelphia, P. Blakiston's Son & Co., 1933, p. 251.

17. Smith, P.: On the Pathology and Treatment of Glaucoma, London, J. & A. Churchill, 1891.

ment of 1,000 healthy adult eyes and of 216 eyes affected with primary glaucoma found the average horizontal diameter of corneas of healthy eyes to be 11.6 mm. and that of glaucomatous eyes to be 11.2 mm., with a larger percentage of small corneas among the glaucomatous patients. He also noted that enucleated eyes blind as a result of glaucoma were characterized by a small globe, a disproportionately large lens, a shallow anterior chamber and a closed filtration angle. Bell [10] found only 2 of 25 glaucomatous eyes in her series to be small. From the 27 pedigrees reviewed by Stokes [1] there was no evidence that hereditary glaucoma is due to congenital microphthalmia. Courtney and Hill's [3] patients with juvenile glaucoma had corneas of normal diameter. The corneal measurements reported by Calhoun,[15] Plocher [4] and Briggs [18] were also normal. Veasey and Shumway [19] found a large lens in a myopic eye with juvenile glaucoma. In Stokes's [1] pedigree the corneal measurements were within normal limits. Anderson [7] from a questionnaire with regard to the size of the cornea in hydrophthalmia found that in a series of 110 eyes only 3 were normal. Fifty-six were very large or had a diameter between 14 and 15.75 mm. In 8 instances the corneal diameter measured 16 mm. or more.

In the family being reported on in this paper, 1 patient, Jean S., had a right cornea measuring 10.5 mm. and a left cornea measuring 10.75 mm. Another had corneas 11 — mm. in diameter, and a third, not seen by us, was reported to have small eyes. There was no tendency to hydrophthalmos or to alteration of the anterior chambers in any member whom we examined.

DEPTH OF ANTERIOR CHAMBER

Bell,[10] reporting a series of cases in which glaucoma developed before the age of 19, found the anterior chamber normal or rather deep in 4, shallow in 6 and obliterated in 1. Five of the cases in which the chamber was shallow were of the acute or congestive type of glaucoma. Deep or normal anterior chambers were reported by Calhoun [15] in his pedigree. Plocher [4] and Korte [20] reported chambers usually deeper than normal. In Berg's [21] pedigree the anterior chambers were normal or slightly deeper than normal. In Stokes's [1] pedigree the anterior chambers were normal. In hydrophthalmia the anterior chamber, as is

18. Briggs, A. H.: Familial Primary Glaucoma in Adults, Brit. J. Ophth. **23**:649-659, 1939.

19. Veasey, C. L., and Shumway, E. A.: Simple Glaucoma in the Young, Ophth. Rec. **13**:15-21, 1904. Shumway.[6]

20. Korte, W.: Beiträge zur Erblichkeit des Glaukoms, Klin. Monatsbl. f. Augenh. **102**:664-668, 1939.

21. Berg, F.: Erbliches jugendliches Glaukom, Acta ophth. **10**:568-587, 1932.

known, is usually deep, sometimes as deep as 12 mm. or more. The average depth in Anderson's [7] cases of hydrophthalmia was 5.75 mm.

Of the family here reported on, no member examined by us showed alteration in depth of the anterior chamber.

HEREDITARY GLAUCOMA AND MYOPIA

Myopia is the most common refractive condition in hydrophthalmia, but it is present usually in only a moderate degree, 1 to 7 D.; it is not as marked as the increased length of the eyeball would suggest. The disparity between the amount of myopia and the axial length of the eyeball has been explained by Parsons [22] as due to: (1) decreased corneal convexity; (2) decreased convexity of the lens due to stretching of the suspensory ligament, and (3) displacement of the lens backward.

In hereditary glaucoma the increased intraocular pressure is very likely a factor in causing myopia because of the stretching of the elastic sclera. This stretching also may be a compensatory factor for a period when there are no prodromal symptoms or visual field changes. It is not known exactly whether such myopia is due solely to the increased intraocular pressure or whether there is a hereditary relationship between the myopia and the glaucoma; the high incidence of myopia in association with hereditary glaucoma suggests that the hypertension produces a distention of the eyeball resulting in a change in the refraction.

In Plocher's [4] pedigree all the 18 members affected with glaucoma were myopic. In Zorab's [23] pedigree 3 of the 7 affected members were myopic. Nettleship's [24] and Somya's [25] patients were myopic. Löhlein [12] found approximately 50 per cent of the glaucomatous eyes in his younger patients to be myopic, while only 15 per cent of his patients with senile glaucoma were myopic. In Haag's [11] group 31 per cent of his young glaucomatous patients were myopic and 17 per cent of them had a myopia of 6 D. or more. Von Graefe [13] observed that one third of his patients with glaucoma simplex were myopic. Fifty per cent of Keerl's [9] patients were myopic, and in 21 per cent of these the myopia was of 6 D. or more. In the pedigrees of Courtney and Hill [3] and Calhoun [15] the patients were practically emmetropic or only slightly myopic. The refraction of 13 of the affected members in Stokes's [1] pedigree was determined, and 8 were myopic and 5 emmetropic.

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22. Parsons, J. H.: Refraction in Buphthalmia, Brit. J. Ophth. **4**:211-216, 1920.

23. Zorab, A.: Glaucoma Simplex Familialis, Tr. Ophth. Soc. U. Kingdom **52**:446-460, 1932.

24. Nettleship, E.: On the Prognosis of Chronic Glaucoma: Glaucoma in Early Life, Roy. London Ophth. Hosp. Rep. **12**:220, 1888.

25. Somya, J. R.: Ueber erbliches Glaukom, Klin. Monatsbl. f. Augenh. **31**: 390-394, 1893.

In our family 2 of the 4 affected members for whom refraction could be done were myopic; 1 had 5 D. of myopia and the other had a variable myopia of 1 to 5 D. in the right eye, which was difficult to control, and myopia of 1 D. in the left eye, which was easily controlled with a single goniotomy.

TYPE OF GLAUCOMA

Reviews of the literature reveal that hereditary glaucoma is usually but not always of a chronic form. Harlan [26] reported on a family in which glaucoma of the congestive type appeared in five successive generations before the age of 20. Von Graefe [13] stated the belief that the acute form is more often inherited than the chronic form. Haag [11] found that in a series of 67 cases the congestive type was twice as frequent as the simple type. Wallenberg [27] observed a rapidly progressive type of glaucoma in a pedigree of four generations; all members had become blind, and the onset occurred at an average age of 22. Biro [28] reported 3 pedigrees of three generations in which an inflammatory type of glaucoma was found. The type of glaucoma in a family usually does not vary, being either congestive or noncongestive, although the two forms have been reported in the same family (Howe,[29] Rogman [30] and Plocher [4]). Lawford [31] found inherited glaucoma usually chronic, as did Stokes [1] in his review of 27 pedigrees and in his own pedigree. Nettleship [24] divided glaucoma of early life into (1) buphthalmos, (2) glaucoma secondary to keratitis or sclerokeratitis, usually in inherited syphilis, and (3) primary glaucoma in children or in adults under 30.

Löhlein [12] tabulated juvenile glaucoma in 1,640 cases; in 18 per cent it was acute and in 82 per cent chronic. In his own series of 140 eyes, 7 had absolute, 24 acute or subacute and 109 chronic glaucoma. Fuchs, in discussing Löhlein's [12] paper, offered the following classification:

1. Chronic glaucoma with a shallow anterior chamber occurring in early life; hereditary and familial.

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26. Harlan, H.: A Case of Hereditary Glaucoma, J. A. M. A. **5**:285-286 (Sept. 12) 1885.

27. Wallenberg, T.: Hydrophthalmus, Deutsche med. Wchnschr. **33**:1275, 1907; Erbliches juveniles Glaukom, Ztschr. f. Augenh. **24**:468, 1910.

28. Biro, I.: Notes on the Heredity of Glaucoma, Ophthalmologica **98**:43-50, 1939.

29. Howe, L.: A Family History of Blindness from Glaucoma, Arch. Ophth. **16**:72-76, 1887.

30. Rogman, A.: A propos de la pathogénie du glaucome chronique simple, Clin. opht. **5**:73-75, 1899.

31. Lawford, J. B.: Examples of Hereditary Primary Glaucoma, Roy. London Ophth. Hosp. Rep. **17**:57-68, 1908.

2. Glaucoma associated with a congenital anomaly, in the same class with hydrophthalmos; also hereditary and familial.

3. Glaucoma with a deep anterior chamber in a myopic eye.

4. Glaucoma with a deep anterior chamber and fine keratic precipitates; secondary.

The members of the family reported on in this paper had a chronic simple type of glaucoma.

ASSOCIATED CONDITIONS

There is surprisingly little evidence in the literature (1) that hydrophthalmia is seen commonly among patients with hereditary glaucoma or (2) that these two conditions are essentially the same disease with the same underlying pathogenesis. Löhlein's [12] report was based on a family of 4 sisters, the youngest having marked hydrophthalmia and glaucoma developing in the other 3 at the ages of 15, 17 and 10. Derby [32] reported on a glaucomatous father, blind for 25 years, with a family of 11 children, 3 blind with glaucoma and 1 with hydrophthalmia. Berg [21] reported a pedigree of six generations with 21 affected members, 19 with chronic glaucoma and 2 with hydrophthalmia. Scheerer [33] reported hydrophthalmia in a father, daughter and cousin and juvenile glaucoma in another cousin appearing at the age of 18. Korte [20] reported on a family in which the father and daughter had glaucoma simplex and hydrophthalmia developed in 2 grandchildren, 1 male and the other female.

The aforementioned association of hydrophthalmia and hereditary glaucoma suggests that the underlying genetic cause of both is probably a failure of development of the filtration angle. Microscopic examination of hydrophthalmic eyes has shown abnormalities of the anterior portions. Examination of excised adult eyes with hereditary glaucoma has been inconclusive because of disorganization of the globes by operation, inflammation or prolonged hypertension.

There was no evidence of a tendency to hydrophthalmia in any of the affected persons discussed in this report.

GONIOSCOPIC FINDINGS

No notes have been found in the literature of gonioscopic study of persons with hereditary glaucoma. Gonioscopic examinations were carried out on the 4 youngest affected members of this family. In 2, on whom gonioscopy was done before any operation was performed, there

32. Derby, H. C.: Three Cases of Hydrophthalmus Treated with Iridectomy, Arch. Ophth. **11**:37-40, 1882.

33. Scheerer: Demonstration klinischer Fälle, Klin. Monatabl. f. Augenh. **89**: 829, 1932.

were found many fine iris processes with finger-like or weblike projections extending anteriorly toward the limbal portion of the cornea. This was the only anomaly we recognized in the chamber angle.

COLOR OF IRIS

The predisposition of dark eyes to glaucoma has been mentioned by many authors. Lange [34] in 1887 quoted Rydel, Rosas, Sichel and von Arlt as believing that glaucoma occurs in brown eyes in the majority of cases. Lange [34] expressed the opinion that the dark iris, with its greater amount of pigment, might be thicker than the light iris and impinge more on the angle of the anterior chamber. Benedict [35] in 1842 reported the case of an elderly man with gout, glaucoma and dark eyes. Two daughters had glaucoma and dark eyes, while a son had gout but was blue eyed and escaped glaucoma.

Of the 5 members of the present family affected with glaucoma, 4 had brown irises and the fifth had blue irises. The other 2 members were not seen by the authors.

HEREDITY AND RACE

Hereditary glaucoma simplex appears as a simple dominant in practically all published pedigrees reviewed by Waardenburg,[36] Franceschetti,[37] Clausen,[38] Bell,[10] Macklin [39] and others. Hereditary glaucoma appears in otherwise healthy stock, and few associated hereditary diseases or anomalies are found in the affected persons. No racial susceptibility has been shown in the literature. The impression that the Jewish race is more susceptible has not been confirmed, since the only pedigree of Jewish ancestry is reported by Kirkpatrick.[40] Consanguinity was reported in 2 pedigrees, that of Plocher [4] and that of Paulo Cezar Pimentel.[2] Stokes's [1] pedigree showed a simple dominant type of heredity with the ratio of affected to normal offspring approximately

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34. Lange: Glaukom und Myopie, Jahresb. ü. d. Leistung. d. Ophth., 1887, vol. 18; cited by Courtney and Hill.[3]

35. Benedict, T. G. G.: Abhandlungen aus dem Gebiete der Augenheilkunde, Breslau, L. Freund, 1842, vol. 1, p. 123.

36. Waardenburg, P. J.: Das menschliche Auge und seine Erbanlagen, in Bibliographia genetica, The Hague, M. Nÿhoff, 1932, vol. 7, pp. 327-343.

37. Franceschetti, A.: Missbildungen und Vererbung, in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1930, vol. 1, p. 712.

38. Clausen, W.: Vererbungslehre und Augenheilkunde, Zentralbl. f. d. ges. Ophth. **13**:41, 1925.

39. Macklin, M. T.: Hereditary Abnormalities of the Eye: Anomalies of Entire Eyeball, Canad. M. A. J. **17**:421, 1927.

40. Kirkpatrick, cited by Bell.[10]

50 to 50. The members of the family here reported were of French-English stock and the ratio of affected to unaffected members was 7 to 8. There was no consanguinity.

PROGNOSIS AND TREATMENT (MEDICAL AND SURGICAL)

There is no evidence in the literature of a favorable outcome without operation, and the results with operation are not certain. The disease cannot be favorably influenced for any length of time by the use of miotics or hypotensive drugs. Germann [41] reported the condition controlled by iridectomy in 2 of 4 patients in a family. Priestly Smith's [17] report was discouraging. Sattler [5] reported the condition checked by iridectomy in 2 patients. Nettleship [24] stated that in 5 patients seen early good results followed iridectomy. Calhoun [15] did 13 operations on 5 patients (9 eyes). He thought that results in patients with early involvement were gratifying and stated the belief that trephining is superior to iridectomy or to the Lagrange sclerectomy with iridectomy. Werner [42] expressed the opinion that a fistulizing operation is superior to iridectomy. In Courtney and Hill's [3] 2 patients, 1 on whom iridectomy had been performed twelve months previously and the other on whom a Lagrange sclerectomy and iridectomy had been performed, the glaucoma appeared to be under control but there was no improvement of vision or fields. In general the best results have been obtained when the operation has been performed early in the disease. Stokes's [1] procedure of choice when the patient was seen during the congestive stage was a puncture of the anterior chamber followed in a few days by an iris inclusion operation (iridotasis). Sclerocorneal trepanation was preferred in those cases in which the eye was free from congestive signs.

Study of the members of our family disclosed that the increased tension responded poorly to miotics alone. Iridectomy and posterior sclerotomy also were not effective. In the left eye in the case of Jean S. one goniotomy was still effective after twenty-nine months. In the right eye five goniotomies, cyclodialysis done twice and a deep root iridectomy were ineffective; an iridencleisis continued to control the condition after 19 months.

Two goniotomies performed a year apart on each eye of a second affected member (Ione S.) were apparently still effective after nine months. In a third member (Miriam S.) one goniotomy on the right eye and two goniotomies on the left eighteen months apart continued to control the condition eighteen months after the first operation. In a fourth member (David S.) a single goniotomy on the right eye remained

41. Germann, D.: Fall von juvenilem Glaukom, Klin. Monatsbl. f. Augenh. **46**: 95, 1908; cited by Courtney and Hill.[3]

42. Werner, S.: Zur Kenntnis des erblichen juvenilen Glaukoms, Acta ophth. **7**:162-168, 1929.

sufficient after twenty months and a single goniotomy on the left continued to control the tension, the visual fields and the vision after eight months.

TECHNIC OF GONIOTOMY AND AFTER-CARE

A thorough study of the chamber angle must be made before any attempt at goniotomy. Schlemm's area must be located. If this area is not seen it is evident that goniotomy will do no good. If the area is recognized one must study the pectinate ligament and the iris processes especially for the purpose of discovering the presence of vessels which must be avoided. The technic of goniotomy has been as follows:

The usual surgical precautions are carried out, such as culture of conjunctival scrapings and irrigation of the nasolacrimal duct. Local anesthesia is produced by instillations of solution of 4 per cent cocaine hydrochloride into the conjunctival sac, and solution of 1 per cent cocaine hydrochloride with ephinephrine is injected subconjunctivally near the area to be incised. The eye is fixed with a forceps, and the goniotomy knife is introduced into the anterior chamber through the limbus at a point approximately 135 degrees opposite the sector of chamber angle to be incised. The blade of the knife is introduced parallel and just anterior to the plane of the iris. With the point of the knife almost touching the pectinate ligament the flat of the blade is made to indent the iris in order that one may again verify the position. Bearing in mind the relative positions as seen with the gonioscope, one can now raise the blade so that the point is in the trabecular area. A sector of one-fifth to one-sixth the circumference of the limbus is *very lightly* incised. The usual site for this surgical procedure has been the lower temporal quadrant, but one must avoid any blood vessels. No contact lens is used, and magnification is provided by a Beebe or a Zeiss loupe. The knife we use has a Barkan cutting point and edge but a cylindric, not a conical, shaft. The cylindric shaft allows easier manipulation without loss of aqueous. The shaft is about 12 mm. long. Usually no mydriatic is used in the postoperative care.

The advantages of goniotomy are that it is simple to perform, is easily repeated if necessary and does not visibly deform or change the appearance of the eye. Its main danger we believe is the possibility of profuse hemorrhage into the chamber caused by too deep cutting or by the cutting of a superficial vessel. This may be avoided by close preoperative study with the gonioscope. A bare nicking of the trabeculae is all that is necessary. The other dangers are similar to those of any other intraocular operation.

No contact glass is used in the operation, as we found that to use one was extremely difficult, complicating the operative technic because the fluid under the glass was frequently lost just as the knife was about to enter the iris angle—sometimes before—and our relationships were thereby disturbed. We have found that operating under the microscope is not as easy as Dr. Barkan led us to think, owing to the difficulty of keeping the point of the knife in focus at all times; the slightest movement of the patient or of the operator causes a blurring of our field or its

complete loss. With the lower magnification of the Beebe or the Zeiss loupe, the operator has greater freedom of action and slight movements of the patient's head or eyes do not destroy the focus or cause one to lose the field.

REPORT OF CASES

First Generation.—Mrs. Anabel O., 71 years old, was an only child. None of her progenitors is known to have had glaucoma. At the age of 8 or 9 years she began to have headaches and saw colored halos about lights. At the age of 14 she had an iridectomy for glaucoma done on each eye by Dr. Daniel A. Thompson, of Indianapolis.

She was not well enough to come to our office for an examination. Her daughter who lived near Chicago stated that she had only enough vision to get around the house and that her eyes were brown and rather small.

Second Generation.—Mrs. David S. (Cecile), daughter of Anabel O., was first seen in our office on Nov. 23, 1940, at the age of 46. Dr. C. C. Clement put at our disposal the record of Dr. Charles H. Beard: "On March 2, 1906, the patient's vision was 20/200 in each eye, corrected to 20/40 with —1.00 D. sph. ⌒ —2.00 D. cyl. axis 90 before each eye. Ophthalmoscopy revealed excavations of the nerve heads of both eyes. The tension was — 1 in each eye. Paracentesis was performed on the right eye on May 24, 1906 and on the left eye on Feb. 3, 1907. Iridectomy was performed on the right eye on April 5, 1907."

Dr. Clement's record stated: "On Nov. 14, 1923, in the right eye the vision was 20/200 and the tension 25 mm. [old Schiötz]; in the left eye the vision was 10/200 and the tension 28 mm. For several years the patient used massage and dropped 0.5 per cent solution of physostigmine salicylate into the eyes during the day and at night. She was not seen again until March 21, 1927, when her condition appeared unchanged."

When we first saw the patient the vision in the right eye was counting fingers at 2 feet (60 cm.) temporally and that in the left eye was light perception and projection temporally. The irises were brown, and there was a broad iridectomy scar extending upward in each eye, with a slight narrowing of the left anterior chamber at the temporal side. The corneas were barely 11 mm. in diameter. The tension was 17 mm. in each eye. Gonioscopic examination revealed a peripheral anterior synechia in each eye extending anteriorly to the cornea; these were at 11 and at 1 o'clock, respectively, near the iris coloboma. Elsewhere Schwalbe's border ring was plainly visible. The fields were unsatisfactory owing to absence of fixation, but they were markedly contracted. Examination in April 1941 revealed no further changes.

Mrs. Inez S., second daughter of Anabel O., 45 years of age, had brown eyes which were not unduly large or small. At the age of 12 years she saw Dr. Frank Morrison, of Indianapolis, who diagnosed glaucoma and urged immediate operation. The parents were under the influence of Christian scientists and would not agree to an operation. The patient never had any treatment for glaucoma and became totally blind at the age of 19.

Third Generation.—Miriam S., born in 1922, daughter of Inez S., began to see halos around lights at the age of 7 years. At 16 she consulted Dr. C. C. Clement because of headaches and he discovered glaucoma to be present. Therapy with miotics was begun at once. The vision in the right eye was 3/200 corrected to 20/50 with —5.50 D. sph. ⌒ —1.00 D. cyl. axis 90. That in the left eye was 8/200 corrected to 20/40 with —5.25 D. sph. ⌒ —1.25 D. cyl. axis 104. The

tension in each eye was 37.5 mm. (Schiötz). After three instillations of pilocarpine hydrochloride in 3 per cent solution the tension came down only two points. The fields were markedly contracted. Gonioscopy revealed the presence in both eyes of many fine iris processes with finger-like projections extending to the corneal limbus, most of them containing tufts of vessels. Therapy with 1 per cent pilocarpine hydrochloride solution dropped into the eyes six times a day was begun, and two days later the tension was 32 mm. in the right eye and 41 mm. in the left. Neosynephrin hydrochloride in a 0.25 per cent solution was used six times, after which the tension was 41 mm. in the right eye and 45 mm. in the left. Goniotomy of the right eye was performed the same day, and goniotomy of the left eye was done three days later. One week after operation on the left eye the tension was 30 mm. in that eye and 26.5 mm. in the right eye. Four days later, with the pilocarpine hydrochloride solution being instilled six times daily in each eye, the tension was 25 mm. in the right eye and 26.5 mm. in the left. The patient was then cared for by Dr. William F. Hughes, of Indianapolis. The visual fields were well maintained, and the tension remained approximately 15 mm. in the right eye and 22 mm. in the left with pilocarpine hydrochloride solution being instilled four times daily in each eye. When the patient was seen after one year the tension was 15 mm. in the right eye and 27 mm. in the left. Goniotomy of the left eye was performed at that time, and eighteen months later the tension had not exceeded 15 mm. in the left eye and 20 mm. in the right. No pilocarpine solution has been used in either eye since the last operation, July 13, 1940.

Ione S., born July 10, 1924, sister of Miriam S., when first seen, July 10, 1939, by Dr. C. C. Clement, at the age of 15 years, had no symptoms and her vision and visual fields were normal but she had a tension of 32 mm. in each eye. She had not known of any increase in ocular tension. We saw her on the same day and found her vision to be 20/20 in the right eye with a correction of $+0.25$ D. sph. $\bigcirc$ $+0.50$ D. cyl. axis 180 and 20/20 in the left eye with a correction of $+0.50$ D. cyl. axis 180. The tension in each eye was 28 mm., and pilocarpine hydrochloride in 1 per cent solution was ordered to be used in the eyes six times a day. Five days later the tension in each eye was 30 mm., with the pupils $1+$ mm. in diameter. After homatropine hydrochloride solution had been dropped in the eyes the tension in the right eye was 33 mm. and the pupil 7.5 mm. in diameter and the tension in the left eye 31 mm. and the pupil 5.5 mm. One per cent physostigmine salicylate solution was instilled once in each eye and 1 per cent pilocarpine hydrochloride solution ordered to be used six times daily. On the following day the tension was 26 mm. in the right eye and 24 mm. in the left. After neo-synephrin hydrochloride in 0.25 per cent solution had been instilled twice the tension was 27 mm. in the right eye and 26 mm. in the left. Two days later, after 5 per cent prostigmine bromide solution had been instilled twice the tension was 26 mm. in the right eye and 21 mm. in the left. With no medication for the following two days the tension in each eye was 28 mm. On July 20, 1940 goniotomy of the right eye was performed at 11 to 7:30 o'clock in the region of Schlemm's canal, a small amount of hemorrhage resulting. Two days later goniotomy of the left eye at 8 to 6:30 o'clock was performed, with only a slight amount of hemorrhage. Three days later the tension was 12 mm. in the right eye and 10 mm. in the left, no drops having been used in either eye since the operation on the left eye. Three months later the patient was again seen, and she stated that the tension had been found one week previously to be 40 mm. in the right eye and 26 mm. in the left. On October 14 a goniotomy of the right eye was performed at 3 to 4:30 o'clock, with very slight bleeding into the

anterior chamber. On the following day goniotomy of the left eye was performed at 3 to 6:30 o'clock, with no bleeding into the anterior chamber. The patient left the hospital on the fourth day with the tension low in both eyes. Three days later it was 20 mm. Gonioscopy of the right eye revealed in the region of the last operation a small opening at 3 o'clock. In the left eye the iris

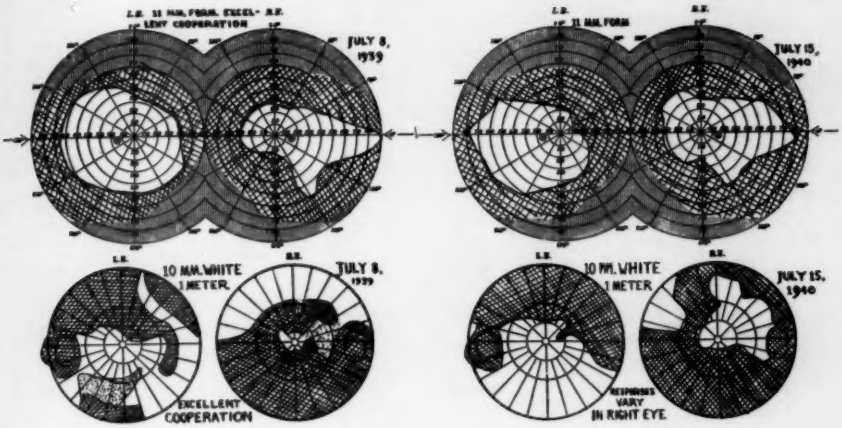

Chart 2.—The visual fields of Miriam S. (third generation).

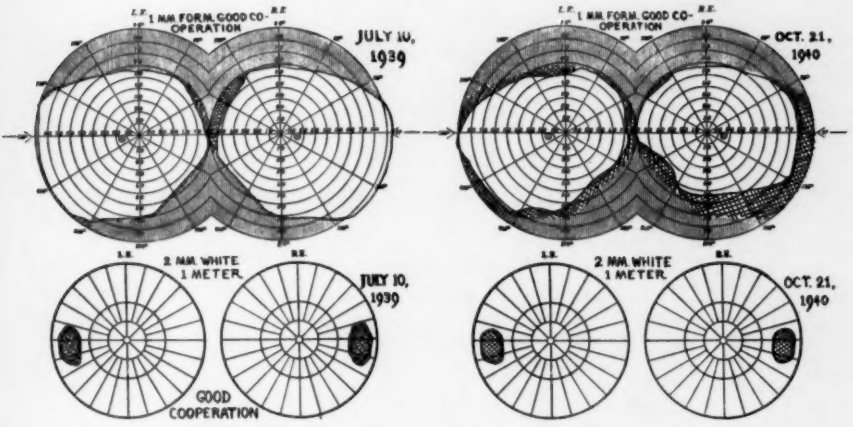

Chart 3.—The tonometric chart of Miriam S. (third generation).

plane was farther back from 3 to 5:30 o'clock, in the region of the last operation. A small slit was present at 4:30 o'clock just anterior to Schlemm's canal. The use of the pilocarpine solution was stopped, and on the following day the tension was 21 mm. in the right eye and 22 mm. in the left. The vision was 20/15 in the right eye and 20/20 in the left. On April 21, 1941 the tension was 15 mm. in the right eye and 21 mm. in the left, pilocarpine hydrochloride solution having been used twelve hours previously in the left eye.

Jean S., born in 1926, son of Mrs. David S., had been examined by Dr. C. C. Clement, whose records stated: "At the age of 7½ years the tension was found to be 39 mm. in the right eye and 43 mm. in the left. The optic disks appeared to contain a normal physiologic cupping, and the fields were normal. The corrected vision was 20/20 in each eye, only a small myopic error being present."

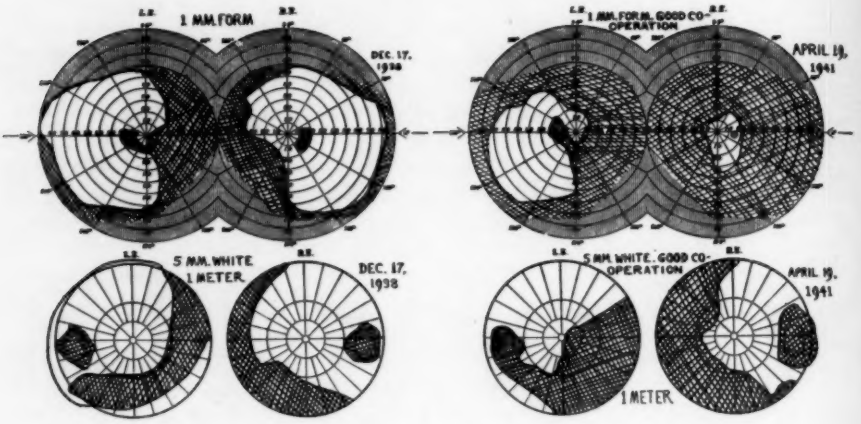

Chart 4.—The visual fields of Ione S. (third generation).

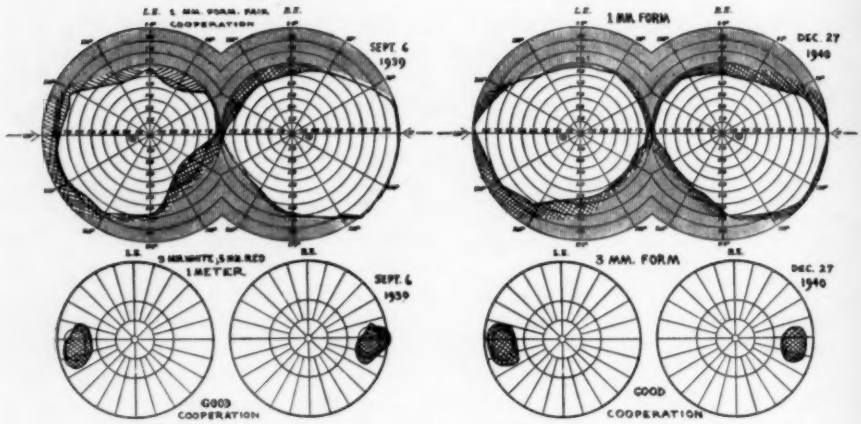

Chart 5.—The tonometric chart of Ione S. (third generation).

The patient was first seen in our office on Dec. 1, 1938, at the age of 12 years. The tension was 41 mm. in the right eye and 49 mm. in the left. The irises were brown; the right pupil was 3 mm. in diameter and very sluggish. The left pupil was 2 mm. in diameter and sluggish. The right cornea was 10.5 mm. and the left cornea 10.75 mm. in diameter. The corrected vision was 20/30 in the right eye and 20/70 in the left eye. The fields were markedly contracted. The optic disks were deeply cupped, with sharp overhanging edges and some atrophy.

Gonioscopy revealed in each eye numerous small weblike extensions coming forward to the cornea and sclera from the iris root. Fifty per cent sorbitol solution (50 cc.) injected intravenously had no effect on the tension. Goniotomy was performed on December 20 on the right eye at 2:45 to 4:15 o'clock and on

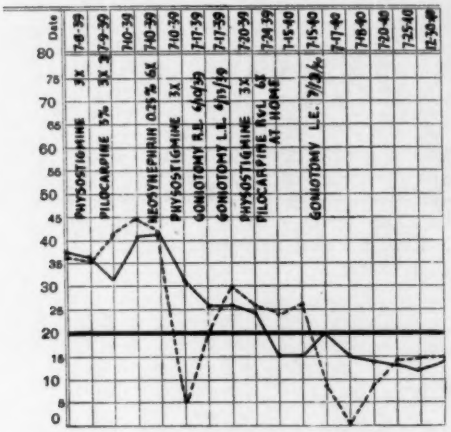

Chart 6.—The visual fields of Jean S. (third generation). In the tonometric charts the unbroken line indicates the right eye and the broken line the left eye.

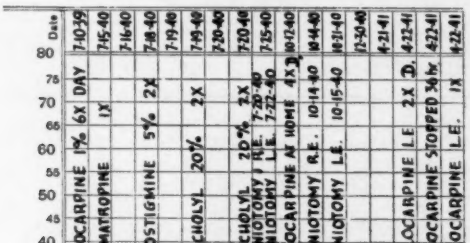

Chart 7.—The tonometric chart of Jean S. (third generation).

December 21 on the left eye at 7:30 to 9 o'clock (inferior nasal quadrant). No further operation on the left eye was necessary. The tension remained below 20 mm. except that on two occasions soon after the operation it was recorded as 25 mm. and 26 mm., respectively. Four more goniotomies were performed on the right eye. Two weeks after the fifth goniotomy there was found a small

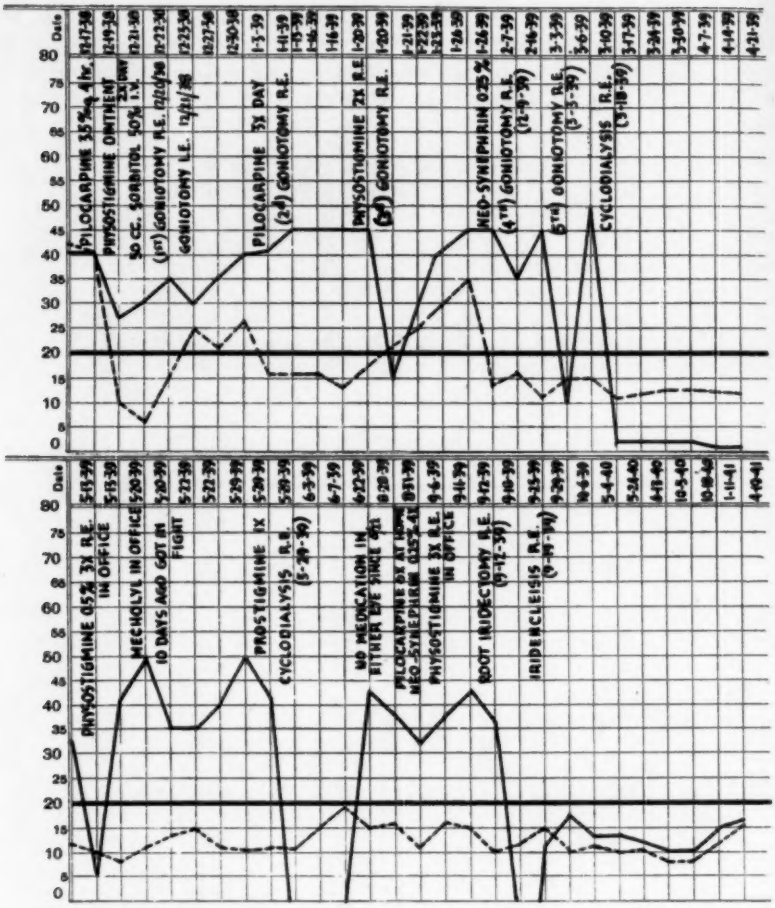

Chart 8.—The visual fields of David S. Jr. (third generation).

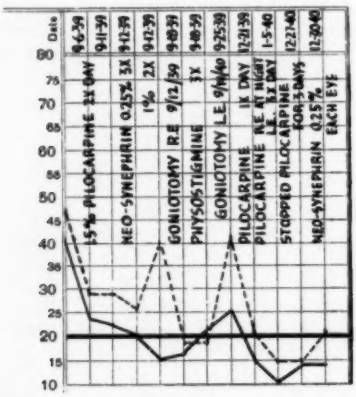

Chart 9.—The tonometric chart of David S. Jr.

prolapse of the iris through the puncture wound in the cornea. Anterior synechias had formed in the region of the goniotomy. March 18, as the tension had returned to 50 mm., cyclodialysis was done at 6 to 9 o'clock. There was a moderate amount of hemorrhage immediately and on the following day, but ten days later the blood had been absorbed. The tension remained low for six weeks, until the patient became angry as a boy smashed an ice cream cone in his face. It then increased to 32 mm. and was raised to 40 mm. by the use of prostigmine bromide. At another time mecholyl chloride caused an increase in tension from 42 to 50 mm. A second cyclodialysis was done at 3 to 7 o'clock. A moderate amount of blood escaped into the anterior chamber. The tension remained low for about three months and then was found to be 44 mm., having been only 15 mm. six weeks before; it was not materially affected by pilocarpine or physostigmine. On September 12 a deep root peripheral iridectomy was done at 10

Operations Performed

M. S.	Right eye:	Goniotomy	6/10/39
	Left eye:	Goniotomy	6/13/39
		Goniotomy	7/13/40
I. S.	Right eye:	Goniotomy	7/20/40
		Goniotomy	10/14/40
	Left eye:	Goniotomy	7/22/40
		Goniotomy	10/15/40
J. S.	Right eye:	Goniotomy	12/20/38
		Goniotomy	1/11/39
		Goniotomy	1/21/39
		Goniotomy	2/ 9/39
		Goniotomy	3/ 3/39
		Cyclodialysis	3/18/39
		Cyclodialysis	5/29/39
		Iridectomy	9/12/39
		Iridencleisis	9/19/39
	Left eye:	Goniotomy	12/21/38
D. S.	Right eye:	Goniotomy	9/12/39
	Left eye:	Goniotomy	9/19/39

to 11 o'clock. This was ineffective. One week later iridencleisis was done at 1 o'clock. For the following nineteen months the tension remained no higher than 17 mm.; the vision with a slight myopic correction (right, — 1.75 D. sph. ⌒ — 1.25 D. cyl. axis 90; left, — 0.25 D. sph. — 2.75 D. cyl. axis 101) was 20/40 ±. No miotic has been used in either eye since September 1939. The patient was last seen on April 26, 1941, when the tension in each eye was 12 mm.

David S., Jr., born in 1918, the older son of Mrs. David S., was first seen, at Dr. Clement's suggestion, on Sept. 6, 1939. He had been watched by Dr. Clement for twelve years, during which time his eyes had tired and watered after near use but there had been no pain or inflammation. Halos had been seen for six years, and these had been somewhat worse in the last two months. He had been using 1.5 per cent solution of pilocarpine hydrochloride for nine years. During that time the tension was seldom above 25 mm. in either eye. We found the vision to be 20/20 — 1 in the right eye with a correction of + 0.88 D. sph. ⌒ + 1.25 D. cyl. axis 180 and 22/20 in the left eye with a correction of + 0.75 D. sph. ⌒ + 1.00 D. cyl. axis 180. Both corneas were normal. The tension was 43 mm. in the right eye and 48 mm. in the left, the pilocarpine solution having

been used twice daily previously. A goniotomy of the right eye was done one week later and was followed by a goniotomy of the left eye two weeks later. After these operations the tension remained under 20 mm. with the aid of drops except on one occasion, when it rose to 26 mm. in the right eye and 42 mm. in the left and was controlled by increasing the administration of the drops from one time to three times daily. Thereafter it remained normal even though the use of drops was discontinued for periods up to three days.

SUMMARY AND CONCLUSIONS

1. Hereditary primary glaucoma is a result of a simple dominant type of heredity and is not sex linked.

2. In the pedigree reported the ratio of affected to nonaffected members was 7 to 8.

3. No evidence of consanguinity was present.

4. The average age of onset was 11.6 years.

5. In all cases the glaucoma was of the chronic simple type.

6. Two of the 4 patients whose error of refraction could be determined had myopia; in 1 this was of more than 5 D. in each eye and in the other there was variable myopia of 1 to 5 D. in the right eye which was difficult to control.

7. Miotics alone are insufficient; the best results are obtained with a combination of both medical and surgical therapy.

8. Early operation, before extensive damage to vision has occurred, is important. Goniotomy is a simple operation which can be easily repeated; the anterior chamber is not abolished and therefore peripheral anterior synechias are not likely to form unless the operation is followed by hemorrhage of considerable blood in the chamber. In this family it was effective without repetition in 4 eyes, apparently effective with one repetition in 3 eyes and ineffective in 1 eye, in which several other operations (five goniotomies, two cyclodialyses and one deep root iridectomy) also were ineffective. Iridencleisis was successful. The main danger in goniotomy is of cutting a large blood vessel, i. e. by going too deeply into the sclera. A bare nicking of the trabeculae is all that is necessary. The other dangers are similar to those of any other intraocular operation.

Dr. C. C. Clement, of Chicago; Dr. William F. Hughes, of Indianapolis, and Dr. James F. Finegan, of Omaha, provided information in regard to certain members of this family.

ABSTRACT OF DISCUSSION

Dr. Paul A. Chandler, Boston: When I was asked to discuss this paper I remembered a family with hereditary simple glaucoma previously reported on by the late George Derby. The original member with glaucoma was blind at the age of 25. There is no record of an examination. In the next generation there were 11 children, of whom 4 were examined and found to have glaucoma. One person in the third gen-

eration and 1 in the fourth had glaucoma. The patients reporting to me for examination were a mother and daughter, of the third and fourth generation, respectively. The mother began to have trouble when she was 15 years of age. She had a bilateral iridectomy which controlled the disease in one eye. A trephination was done later in the other eye, and the disease was thereafter under control in both eyes. The physician who took care of this patient examined her son and daughter, and as a result the glaucoma was discovered in the daughter at the age of 15. She had had a bilateral trephination ten years before I saw her. When she came to me I discovered that one eye was still normal but that in the other eye the tension was 40.

When one sees a patient with primary glaucoma one has two duties to perform: to treat the patient and to see that he follows the treatment recommended. It is the ophthalmologist's duty not to lose sight of him. In the cases cited this duty was carried out. Whenever one sees a patient under 40 with primary glaucoma it behooves one to see that the other members of the family are examined in the hope of detecting the disease in an early stage.

With regard to treatment, a consideration of all reports must inevitably lead to the conclusion that an operation should be performed early and that a filtering operation is the most effective procedure.

Dr. Thomas D. Allen, Chicago: I have been asked just what our technic was. I think it would be better for you to come to me separately so that I can talk the matter over with you than to take up your time now. Some of you may not be particularly interested.

Goniotomy is a rather difficult operation as proposed by Dr. Barkan. It has to be done under a contact glass and with considerable magnification. As a result the field is not easily kept in focus. In the operation as we do it the field is kept in focus all the time but we do not get such high magnification, and we do not see the actual point of the knife although we see the blade; by studying the eye before the operation is done, we know in just what position we are.

When I tried to teach the operation to my students at the Illinois Eye and Ear Infirmary, I found that their chief mistake was in making too deep a cut. This almost always will bring considerable hemorrhage. Usually the hemorrhage is not overwhelming, but it is disconcerting because a bare nicking of the trabeculae is all that is necessary.

Note.—Since the reading of this paper, an additional member of the family, an 8 year old girl belonging to the third generation, has been found to be affected. The tension was 30 mm. in each eye and not affected by miotics but entirely controlled by a single goniotomy in each eye.

OPERATIVE TREATMENT OF CONGENITAL SUBLUXATION OF THE LENS

ARNOLD KNAPP, M.D.
NEW YORK

Congenitally ectopic lenses need no treatment as long as the vision can be brought up sufficiently by refractive correction through the lens or through the aphakic area. Vision through the lens is generally impossible to correct, because of the deformity of the lens and the marked astigmatism. The correction through the aphakic portion of the pupil depends on the size of this area. It frequently is insufficient. The subluxation of the lens may remain stationary, giving rise to no symptoms beyond the loss of vision; the ectopia may increase in later years, allowing better vision, or total dislocation may occur. More frequently, however, the condition gives rise to cyclitis and glaucoma.

When satisfactory vision in a congenitally subluxated lens cannot be obtained by refractive means, operation is indicated. The operations that come under consideration are iridectomy and discission. A satisfactory iridectomy is not easy to perform and does not prevent possible later complications. Discission, therefore, has usually been practiced. The difficulty of discission is that the lens eludes the point of the knife. Owing to the ball-like shape of the lens the tension of the capsule is slight; the opening in the capsule does not remain open, and, notwithstanding repeated punctures, frequently no opacity results. The absorption of the lens is always slow. A good result follows when the needled lens finally turns opaque and shrinks, thereby enlarging the aphakic area.

Sattler[1] reported on previously published observations and on 3 children on whom he performed discission. He described the difficulties of the operation, which had to be repeated several times although he finally obtained a satisfactory result. His technic was as follows: A sickle-shaped needle or a narrow Graefe knife was introduced opposite the dislocated lens, and the point of the knife was advanced to a point posterior to the opposing pupillary margin. In 1 instance the needle was introduced through the flat part of the ciliary body and then advanced between the iris and the lens into the anterior chamber.

Read at the Seventy-Seventh Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., May 29, 1941.

1. Sattler: Ueber operative Behandlung der Ektopia lentis congenita, Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch., 1897, p. 233.

Haab,[2] in his excellent little textbook on surgery of the eye, said that the subluxated lens had best be needled, particularly in adolescents. His procedure consisted of puncturing the lens with one discission needle in order to fix it and then using the second needle to tear the capsule. This should be done by scleral puncture to avoid immediate prolapse of the vitreous. If the absorption is delayed the needle (either one or two needles) can again be introduced in the opening in order to stir up the lens substance. Satisfactory results were obtained in this way, though the treatment was somewhat prolonged. Haab claimed that this method is particularly indicated in cases of ectopia in which the lens wavers, in which cases glaucoma or luxation is to be feared, and is preferable to extraction of the lens.

In my opinion discission with two knife needles should be performed according to the plan of the Bowman operation. One knife needle is introduced through the sclera just posterior to the limbus at a point opposite the free border of the lens. The free border of the lens is punctured at this point, and the instrument is held firmly in place. Another knife needle is then introduced through the sclera just below the site of the previous puncture, and it perforates the lens capsule at the same point as the first needle did. By approximating the two handles of the knife needles and passing one handle over the other, one separates the two knife blades and enlarges the opening made in the capsule. The needles are then cautiously extracted in turn. This procedure is followed by an opacification of the adjoining part of the cortex, and some of the cortex may be present in the anterior chamber. When the opacification comes to a standstill, the procedure has to be repeated, and it has to be repeated until opacification and shrinkage of the lens have taken place and a clear aphakic area results.

While I have operated on a few patients with satisfactory results, I have only 1 patient whom I was able to follow for as long as eleven years. Her case history follows:

J. K., a girl, was 10 years of age when seen in 1929. She had a history of poor sight due to bilateral subluxation of the lenses. Otherwise she was normal, and there were no familial abnormalities. The vision was 15/200 in the right eye and 10/200 in the left. The pupils were elongated downward, and the lenses were dislocated upward and in. After dilation the vision was not improved in the right eye and was improved in the left eye with + 12 D. sph. to 20/70. It was therefore decided to operate on the left eye, and a simple discission was attempted, without success, on June 24, 1929. The double needle operation described was performed a week later. The lens became partially opaque, and a small piece of cortex protruded into the anterior chamber. The operation was repeated three

2. Haab, O.: Atlas und Grundriss der Lehre von den Augenoperationen, Munich, J. F. Lehmann, 1904.

weeks later. The lens bag gradually shrank, and on July 10 vision with a cataract glass was 20/50. On September 15, after an infection of the upper respiratory tract, the eye became red and iridocyclitis developed and was followed by neuroretinitis. This condition slowly responded to injections of milk and to sweats induced by pilocarpine hydrochloride, and the vision gradually increased to 20/30—. The cataract had shrunk to a small mass nasally, to which the iris was adherent. When the patient was last seen, on June 24, 1940, the vision with a lens was 20/20— and the eye seemed perfectly healthy.

Clinical Notes

VISUAL ACUITY IN THE INDIGENT

HARRY M. SILVERBERG, M.D., BROOKLYN, N. Y.

The accompanying table is an analysis of 1,000 consecutive refractions with particular emphasis on visual acuity. Records of 1,000 patients were taken from the Department of Welfare of New York City. These patients were on home relief and were 18 years of age or older. An attempt was made to see what effect if any poor nutrition and other results of poverty had on their visual acuity and in the production of pathologic change.

The Visual Acuity of 1,000 Indigent Persons

Age Group	Number of Patients	Normal Visual Acuity, %	20/20 with Glasses, %	Type of Error		Gross Pathologic Change, %
				Hyperopia, %	Myopia, %	
18-29	46	13	84.5	28	50	13
30-39	48	16.5	57.5	43	39.5	10
40-49	154	24	56.5	57	19	14
50-59	248	23.5	61.5	66.5	8	14
60-69	303	15.5	62	66.5	10	17
70-79	175	8	58	65.5	13.5	13
80-89	23	8.5	39	69.5	13	43
90-99	3	0	33	66.5	0	66.5

COMMENT

1. The age groups 18 to 29 and 30 to 39 contained the highest percentages of persons with myopia, viz. 50 and 39.5.

2. Visual acuity without glasses was best at the ages of 40 to 49 and 50 to 59, the percentages of persons with normal visual acuity at these ages being 24 and 23.5. After 60 the visual acuity showed a decided drop. In other words, glasses for distance vision were especially indicated after 60 to keep the visual acuity within normal limits.

3. The group 18 to 29 contained the highest percentage of persons with normal visual acuity with correction: 84.5. Among the groups between 30 and 79 the percentages of persons with normal visual acuity with correction were remarkably uniform (56 to 61 per cent); then the percentage dropped to 39.

4. The percentage of persons with pathologic change was also unusually constant for the groups between 18 and 79 (13 to 17 per cent), and then it rose precipitately to 43 at 80.

CONCLUSION

From these figures it would seem that visual acuity is a vital function and is not impaired by poor economic circumstances. Also, the constancy

of the percentage of pathologic change would seem to show that other factors than nutrition must be considered etiologic, as this percentage is about the same as one finds in private practice.

NEW MASK FOR OPERATIONS ON EYE MUSCLES

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In any operation for muscular deviation one of the most disturbing factors to the surgeon can be traced to the type of face covering generally in use. For the surgeon to observe how much of the deviation has been corrected at any time during the course of the operation, the entire sterile face covering must be removed. Such is the construction of the mask in use that no alternative is possible; the mask is little more than a cloth having a hole just large enough to expose one eye and its lids.

When the operation has been performed on one or two muscles, the surgeon usually desires to see how much of the deviation has been corrected. If he is to observe his progress, however, the face covering must be removed, and it is thus rendered unsterile. To proceed to another part of the operation, the surgeon must now either use an unsterile cloth or discard the first cloth and use another, sterile one. As often as he desires a simultaneous view of both eyes, the same difficulty of the unsterile mask presents itself.

Even more objectionable is the time consumed in removing and replacing the face covering during the course of the operation. Each simultaneous view of both eyes necessitates the removal, the replacement and the readjustment of the face covering. The steady progress of the operation is disrupted no matter how fleeting is the surgeon's glance. As a result, the tendency has been to observe the progress of the operation as infrequently as possible.

It was my purpose, therefore, to devise a face covering which would eliminate this difficulty in operations on the muscles. The face covering here presented is so designed that it need not be removed at any time during the course of the operation; either one eye or both eyes can be covered or uncovered at will without disarranging the entire mask. The mask consists of two adjacent rectangular openings each large enough to expose one eye. These two openings are connected by a strip of cloth just wide enough to cover the nose. At the temporal side of each opening there is a flap large enough to cover that opening. It is this arrangement of two openings, each provided with a cover, which permits the exposure of each eye individually or of the two eyes simultaneously.

In the making of this face covering, two problems have to be met in order that difficulties and inconveniences may be avoided. The flaps must open and close readily, and they must, moreover, remain as they are placed without clips, pins or other fastenings. In the mask which I have used, these difficulties are avoided in the following manner: The rectangular holes are cut along only three sides—the upper, the lower and the nasal sides—so that the cut rectangle of cloth hangs away

temporally. The uncut side of the hole forms a natural hinge, which moves readily back and forth. The dangling pieces of cloth form the bases of the flaps. A relatively wide binding is sewn around the rudimentary flaps, and the weight of the binding is itself sufficient to hold the flaps in place either open or shut. The binding is made wide enough so that each flap will completely cover its opening and small enough so that the flaps will meet at the center of the nose piece and not interfere with each other.

The dimensions and the design of this new face covering are shown in figure 1. These dimensions can, of course, be varied and they are of

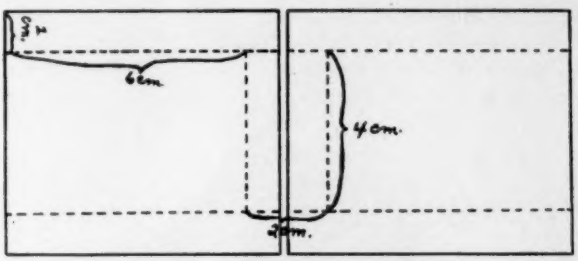

Fig. 1.—Diagram of the new mask.

Fig. 2.—The mask in position.

no special significance. Depending on the surgeon's choice, the flaps may be placed either temporally or at the upper borders of the openings. It has been my experience that when the flaps are placed temporally they remain in position much more readily than when they are placed at the upper borders. Even more important, temporal flaps do not interfere with the surgeon's fingers while he is operating. The mask in position is shown in figure 2.

Not only has this operative face covering proved successful in eliminating the nuisance of constantly removing and readjusting the mask, but, most important, it has proved to be time saving during any operation for muscular deviation. It is presented primarily with this point in mind.

STUDY OF LIGHT PERCEPTION AND PROJECTION WITH A NARROW BEAM OF LIGHT

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Perception of light and recognition of its projection in an eye with cataract may be investigated by means of a beam of light 2 or 3 mm. in diameter directed from a distance of 36 cm. The apparatus employed is the ordinary ophthalmologic lamp, but this has a circular opening 2 or 3 mm. in diameter which throws out a fine beam of light (fig. 1). With the lamp placed beside the head of the patient, this beam is received by a concave mirror 36 cm. from the eye with the cataract (fig. 2); the mirror reflects the beam toward that eye. The beam must be directed

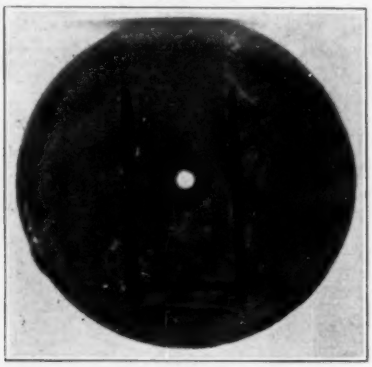

Fig. 1.—Front view of the common lamp, showing the central circular opening 2 to 3 mm. in diameter through which passes the fine beam of light which, received by the concave mirror, is projected toward the eye with cataract.

from in front, from above and below and from inside and outside in order that the perception of light by the posterior, lower, upper, external and internal segments of the retina may be investigated. The examination may also be performed with the mirror in front but the gaze of the eye with cataract directly upward, downward, inward and outward. The results with this procedure are accurate, much more so than those with the old procedure (still used in some clinics), in which the flame of a match at a distance of 5 cm. illuminates the eye diffusedly. With the beam of light used in the way described it is actually possible to learn whether all sections of the retina perceive the light, because the beam falls in the shape of a narrow ray on each and is not diffused, as is the light of a match.

The concave mirror must be placed 36 cm. from the eye being examined because at a longer or at a shorter distance the beam of light projected is of a larger diameter than 2 or 3 mm.

In an eye with cataract the blindness in parts of the retina due to a previous loosening of the retina or to some other cause, such as a tumor, is discovered more easily by this method than by the old ones, such as the use of a candle at 5 meters.

The patient must be instructed to say "Light!" as soon as he realizes that the eye has been impressed by the bright ray.

The test may be repeated many times for the checking of results.

When green, red, blue or yellow glass is inserted in the opening of the source of light the patient with ripe cataract will be able to tell the

Fig. 2.—Correct placing of the source of light with regard to the patient and the observer, the latter holding the concave mirror 36 cm. in front of the former.

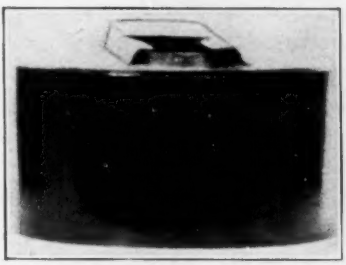

Fig. 3.—Side view of the lamp, showing the slot support in which the colored glasses are fitted for the investigation of the perception of a colored beam of light and recognition of its projection.

color of the ray that reaches the eye. Fuchs and Salzmann [1] said: "In cataract visual alteration is dioptric; that is to say, it affects the keenness of sight but not the sense of color."

According to these authors the patient with cataract must have, besides good perception of light and recognition of its projection, good perception and ready recognition of color if he is to be operated on.

1. Fuchs, E., and Salzmann, M.: Diseases of the Eye, translated by E. V. L. Brown, ed. 10, Philadelphia, J. B. Lippincott Company, 1933.

Study of the perception of color and the recognition of its projection may be carried out with the apparatus described by placing successively transparent red, green, yellow and blue glass immediately before the circular opening. The glass should fit into a support, slot or other fixtures mounted on the lamp itself (fig. 3).

I have ascertained that patients with ripe cataract most readily recognize a red beam of light.

In the literature various methods of studying the perception of light and the recognition of its projection are described, as follows: Argañaraz [2] stated that these functions "may be investigated with the flame of a candle." Duverger stated that an eye with advanced or complete cataract may perceive the light of a bulb at 5 meters and Terrien that the eye may see this light at 2 or 3 meters. Poulard [3] wrote that it "may see the light from a luminous source placed at a distance of 1 or 2 meters." Fuchs and Salzmann,[1] declared that "the light of a bulb may be perceived at a distance of 6 meters."

In the Service of the Chair of Ophthalmology in the City of Córdoba, Argentina, the perception of light and the recognition of its projection are investigated with the light directed at a distance of 5 meters from the eye with cataract.

These differences according to different authors in the distance at which the patient with cataract can perceive light are in my opinion due to slight differences in the density of the opacity and in the size of the frontal-posterior, vertical and horizontal diameters of the crystalline lens in different subjects with ripe cataract.

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2. Argañaraz, R.: Oftalmología para médicos prácticos y estudiantes, Buenos Aires, 1929.

3. Poulard: Traité d'ophthalmologie, Paris, Masson & Cie, 1923, vol. 1 and 2.

Ophthalmologic Reviews

EDITED BY DR. FRANCIS HEED ADLER

ETIOLOGY OF DACRYOCYSTITIS AND EPIPHORA

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The lacrimal sac is subject to acute and to chronic inflammation. The primary lesion in either condition is usually not in the sac but in the nasolacrimal duct in the form of an obstruction. On account of the obstruction of the duct there is interference with the normal flow of tears through the sac. The tears, with their bacterial content, are retained, and inflammation follows in the sac. The contents of the sac are augmented by a mucopurulent secretion from the inflamed mucosa; then the sac becomes dilated and the walls thickened. The distention is known as a mucocele. The enlarged sac forms a visible and palpable tumor below the inner end of the lower eyelid. Pressure on this will usually cause regurgitation into the conjunctival sac or, less often, into the nose. Irrigation of the sac through the punctum and the canaliculus causes the contents to be washed into the conjunctival sac. Epiphora and the presence of a mucopurulent discharge are prominent symptoms. This is a typical picture of chronic dacryocystitis. The enlarged sac is susceptible to attacks of acute inflammation from slight trauma, from the presence of especially virulent organisms in the sac or from no apparent cause. It is a real menace to the eye, because a slight corneal abrasion may become infected by its contents and any accidental or operative wound of the eyeball is even more likely to become infected.

Diseases of the nasolacrimal passages originate frequently in the nose, rarely in the eye and less frequently from disorders of the surrounding tissues, such as infiltrative disease, bone-destructive processes and trauma. Dacryocystitis may be due to obstruction in any part of the nasolacrimal canal or in the sac itself or may be nonobstructive but contingent on other conditions.

CONGENITAL FACTORS

Granström [1] stated that congenital closure of the ostium of the nasolacrimal duct is not rare and is usually associated with dacryocystitis.

From the Aural Service of the Boston City Hospital.

1. Granström, K. O.: Die Dakryozystitis bei Kindern, Acta ophth. **16**:512, 1938.

Rigler [2] expressed the opinion that dacryocystitis is the result of delayed canalization, which in 95 per cent of cases occurs in the nasal end of the canal. Kramer [3] likewise stated the belief that congenital dacryocystitis originates not through infection but as the result of an imperforate lower end of the nasolacrimal duct. Schaeffer [4] expressed the opinion that all disease processes in infants and in adults which lead to either a partial or a complete obstruction of the lumen of the lacrimal canal are in a measure contingent on irregular canalization or complete absence of the canal. Defective canalization, he said, frequently leads to the formation of folds, flaps and diverticula in the mucous membrane, especially in the middle portion of the nasolacrimal canal. The same investigator stated that the inferior opening of the nasolacrimal duct may be so small that it cannot function, may pass through the nasal mucous membrane rather obliquely or may be slitlike and in a sense merely potential.

In the examination of 20 full term fetuses, Fiori-Ratti [5] found the inferior opening closed in 6. In fetuses of less than full term he found that the Bochdalek flap was always imperforate. In 6 of 15 infants 9 months of age he found it closed. Ferrer [6] reported a case of dacryocystitis in an infant due to obstruction of the valve of Hasner by a fold of mucosa. I have had under my care a 3 month old infant in whom marked dacryocystitis appeared five days after birth. The condition was relieved by perforation of the membrane at the nasal end of the lacrimal duct.

Pseudoconjunctivitis present at birth or immediately afterward has been reported by Weil [7] and Peters.[8] They attributed it to failure of spontaneous rupture of the inferior lacrimal ostium. The sac becomes distended with cellular debris, infection ensues and purulent secretion is conveyed by the canaliculi to the conjunctiva.

In children from 1 to 10 years of age dacryocystitis is considered by Granström [1] to be due to neglected congenital stenosis of the naso-

2. Rigler, L. W.: The Treatment of Congenital Dacryocystitis, J. A. M. A. **81**:23 (July 7) 1923.

3. Kramer, R.: Zur Aetiologie der Dakryocystitis congenita, Ztschr. f. Augenh. **49**:20, 1922.

4. Schaeffer, J. P.: The Nose, Paranasal Sinuses, Nasolacrimal Passageways, and Olfactory Organ in Man, Philadelphia, P. Blakiston's Son & Co., 1920.

5. Fiori-Ratti: Rapporti tra le lesioni delle vie lacrimale e quelle del naso e cavista annesse, abstracted, Monatschr. f. Ohrenh. **50**:153, 1916.

6. Ferrer, H.: Dacriocistitis neonatorum, Vida nueva **25**:207, 1930.

7. Weil, G.: La pseudo-conjonctivite du nouveau-né, J. de méd. de Paris **25**: 557, 1931.

8. Peters: (*a*) Die Beteiligung der Nebenhöhlen der Nase bei der Tränensackeiterung, Klin. Monatsbl. f. Augenh. **21**:767, 1913; (*b*) Ergebnisse der Nasenuntersuchung, München. med. Wchnschr. **52**:147, 1905.

lacrimal duct. He reported 36 cases of infection of the lacrimal passages in children, in 25 of which the condition was due to congenital stenosis. Of these the infection occurred in the first year in 21, in the second year in 3 and in the seventh year in 1.

ANATOMIC FACTORS: ASSOCIATION OF GENERAL NASAL DISEASE WITH DACRYOCYSTITIS

In the acquired type of dacryocystitis there is frequently obstruction of the lower part of the nasolacrimal duct. For this reason it is often inferred that disease of the lacrimal passages has its origin in the nose. The anatomic condition of the nasolacrimal duct, as has been shown by Schaeffer,[4] is frequently an etiologic factor in its obstruction. His investigations indicate that many nasolacrimal ducts present lumens of very irregular contour, some even being more or less tortuous in course. Apart from this type of irregularity, diverticula, or direct outpouchings of the nasolacrimal duct, are not uncommon. The same author stated that because of the intimate anatomic relationship that exists between the nasolacrimal passages, the nasal fossa and the nasal sinuses, disease of the sinuses is frequently the etiologic factor in dacryocystitis. At best, he stated, only a paper-like lamina intervenes between the ethmoidal cells and the lacrimal sac and the nasolacrimal duct. Congenital dehiscences of the bony wall between the nasolacrimal duct and the maxillary sinus are not infrequently observed. (I myself have observed them.) Jacod[9] expressed the opinion that the anatomic features mentioned plus infection from the nose are the main etiologic factors in dacryocystitis.

Post[10] stated that ascending infection is the underlying cause in practically all cases of chronic dacryocystitis. He expressed the belief that this in association with mechanical obstruction in the nose produces ideal conditions for the development of dacryocystitis. Rollet and Bussy[11] removed the lacrimal sac and its duct together in 100 cases of dacryocystitis for the purpose of anatomicopathologic study. (They did not state whether the sacs were removed from living patients or from cadavers.) They described, photographed and made serial sections of the sac and its duct. In 43 per cent of their cases they found the lower

9. Jacod, M.: Le larmoiement sans sténose et l'obstruction mécanique de l'orifice inférieur des vies lacrymales, Ann. d'oto-laryng., 1932, p. 562.

10. Post, L. T.: The Treatment of Chronic Dacryocystitis, editorial, Am. J. Ophth. **11**:63, 1928.

11. Rollet, and Bussy, L.: (*a*) Recherches anatomo-pathologiques sur cent cas de dacryocystites avec extraction du sac et du canal, Arch. d'opht. **40**:321, 1923; (*b*) Ectasies et sténoses des voies lacrymales, Lyon chir. **20**:293, 1923; (*c*) Recherches bactériologiques et cliniques sur cent dacryocystites avec ectasie du sac, Arch. d'opht. **40**:5, 1923.

segment of the nasolacrimal duct obliterated. They stated the opinion that the lower half of the nasolacrimal duct is especially predisposed to disease which has its origin in a similar disease process in the nose.

Halle,[12] on the other hand, said that the stenosis is in most cases at the junction of the lacrimal sac and the nasolacrimal duct and proceeds from there to the sac. Huchat [13] stated that as a result of his studies he was of the opinion that 93 per cent of disease of the lacrimal sac is of nasal origin. Heinonen [14] examined the lacrimal drainage apparatus of 299 private patients by the rhinologic and fluorescein method. Of 196 who had from mild to complete lacrimal obstruction, 136 presented various pathologic changes in the nose. In 103 the lacrimal drainage was normal although there were pathologic changes in the nose. The same author by measuring the nasal skeleton could demonstrate in numerous instances a rise of the nasal index value [15] in women sufferers. In women the nasal index was higher on the average than in men; the index was also relatively high in cases of bilateral disease of the lacrimal passages. Urbanek [16] in over 100 operations on lacrimal sacs found nasal complications so often that he no longer considered it good practice to treat blenorrhea of the lacrimal sac without first making a careful study of the nose. Fiori-Ratti [5] reported 101 cases of disease of the lacrimal passages in association with various pathologic conditions in the nose or sinuses as follows: hypertrophic rhinitis, 27 cases; vasomotor rhinitis, 21 cases; syphilitic rhinitis 11 cases; rhinitis ozaenosa, 10 cases; adenoids, 6 cases; eczema of the nares, 7 cases; purulent rhinitis, 4 cases; nasal trauma, 2 cases; ethmoiditis, 4 cases; maxillary sinusitis and ethmoid tumor, 2 cases; nasal tumor, 4 cases; atrophic rhinitis sicca, 1 case, and rhinitis fibrinosa, 1 case; in 2 cases there was no nasal disease. Kuhnt,[17] Paterson [18] and Malling [19] expressed the opinion that diseases of the nose and of the sinuses are of

12. Halle, M.: Intranasale Tränensackoperation bei Säuglingen, Med. Klin. **24**: 1631, 1928.

13. Huchat, cited by Kofler.[21a]

14. Heinonen, O.: Klinische Untersuchungen über die Bedeutung der Nasenkrankheiten und einige disponierende Momente in der Aetiologie der Dakryostenose Klin. Monatsbl. f. Augenh. **65**:610, 1920.

15. The nasal index value: $\frac{\text{Width} \times 100}{\text{height}}$

16. Urbanek, J.: Die Indikationstellung zur Dakryocystorhinostomie, Wien. med. Wchnschr. **77**:1109, 1927.

17. Kuhnt, H.: Ueber die Behandlung von alten Tränensackleiden, Zentralbl. f. d. ges. Ophth. **1**:30, 1914.

18. Paterson, D. R.: The Intranasal Treatment of Lacrimal Disease, J. Laryng. & Otol. **29**:169, 1914.

19. Malling: Bedeutung der Nase bei Tränenwegleiden, Deutsche med. Wchnschr. **46**:28, 1920.

great etiologic importance in all forms of disease of the lacrimal passages from simple epiphora to the most severe phlegmonous type. They stated that in their opinion 95 per cent of disease of the lacrimal apparatus is of nasal origin.

VASCULAR AND LYMPHATIC RELATIONS

The abundant network of lymphatic vessels is vitally important in establishing relations between the mucous membrane of the nasal and of the nasolacrimal fields. Also, the dense venous plexuses of the nasal mucous membrane establish connections with the venous plexuses of the paranasal sinuses and the plexuses surrounding the lacrimal sac and the nasolacrimal duct. The venous plexuses of the nasolacrimal passages connect also with the facial, infraorbital and ophthalmic veins. Zuckerkandl [20] has demonstrated a lacrimofacial vein connecting with a larger vein emerging from the region of the anterior ethmoid cells and passing through the lacrimal bone. These anatomic features may be of great importance in the extension of disease from the nasal fossa and the related nasal sinuses to the lacrimal sac and the nasolacrimal duct and vice versa.

IRRITATIVE AND INFLAMMATORY CONDITIONS OF THE NOSE

Kofler [21] stated that irritative conditions of the nose, whether vasomotor or inflammatory, may cause a variable degree of obstruction in the opening of the lacrimal canal and from there spread to and involve the membranous portion of the canal and thus produce complete obstruction of the entire lumen. Sondermann [22] said that chronic inflammation of the mucous membrane with enlargement of the inferior turbinate may be a frequent cause of constriction of the lacrimal canal. He cited particularly the presence of chronic catarrhal conditions in children associated with marked swelling of the nasal mucosa caused mainly by adenoid vegetations. Bogendörfer [23] reported 2 cases of suppuration of the lacrimal sac cured by removal of the adenoids. The same author reported 4 cases in which epiphora was caused by swelling of the inferior turbinate.

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20. Zuckerkandl, cited by Schaeffer.[4]

21. Kofler, K.: (*a*) Beziehungen der Tränensackleiden zur Nase und ihre Behandlung, Ztschr. f. Hals-, Nasen- u. Ohrenh. **27**:31, 1930; (*b*) Rhinogene Erkrankungen der unteren Tränenwege, Wien. klin. Wchnschr. **23**:352, 1919; (*c*) Tränensackeiterung bei Ozaena, Monatschr. f. Ohrenh. **61**:377, 1928.

22. Sondermann, R.: Beitrag zur Klinik der Tränenwege, Klin. Monatsbl. f. Augenh. **70**:474, 1923.

23. Bogendörfer, L.: Ueber die Beziehungen der Tränenwege zur Nase, Internat. Zentralbl. f. Laryng. **35**:3, 1919.

PRESSURE ON THE OSTIUM

Pressure on the ostium of the nasolacrimal duct may lead to constriction or entire closure of the lacrimal canal. This pressure may be the result of hyperplasia of the nasal mucosa. Bohm [24] reported 10 cases of such involvement among 84 cases of dacryocystitis. According to Paterson,[18] the same condition may be brought about by simple or papillary hypertrophy, which may be either circumscribed or diffuse; by polyps, cysts or marked septal deviation, or by circumscribed changes in the mucous membrane.

The most favored site for the origin of diffuse papillary hypertrophy, in the opinion of Bilancioni,[25] is the posterior end of the inferior turbinate. The hypertrophy usually remains limited to this turbinate, seldom spreading to the floor of the nose or to its passages. The septum is rarely involved. Bilancioni described a patient in whom the hypertrophy had spread to involve the inferior meatus and the floor of the nose so that the entire nasal cavity was obstructed by the proliferation. The outlet of the lacrimal canal was involved in the same hypertrophy. This resulted in marked epiphora, with reddening of the bulbar conjunctiva. Kofler [21] stated that it is surprising that this disturbance is not observed more often, since one frequently encounters hypertrophy of the inferior turbinate. In his opinion, the explanations are (1) that the mucous membrane covering the upper portion of the inferior turbinate is thin and delicate and (2) that the position of the inferior turbinate and its convexity toward the septum is such that the upper portion of the inferior meatus, where the exit of the lacrimal canal is found, is wider than the lower part.

It has been suggested by Stenger [26] that dacryocystitis is contingent on two factors: (1) abnormal enlargement of the nasolacrimal ostium and (2) mechanical extension of infected secretions into the lacrimal ducts from the nose.

Fiore [27] has produced in rabbits changes in the lacrimal passages, the conjunctiva and the cornea after complete packing of one side of the nose. He made the assertion that protracted tamponade of the nose results in closure of the lacrimal passages and that bacteria may enter

24. Bohm, F. M.: 84 Fälle von Dakryocystorhinostomie nach Toti, Klin. Monatsbl. f. Augenh. **66**:454, 1921.

25. Bilancioni, G.: Ipertofia papillare diffusa di tutto il tratto inferiore della mucosa nasale, Arch. ital. di laring. **41**:72, 1921.

26. Stenger: Beziehungen von Augenleiden zur Erkrankungen der Nase und der Nebenhöhlen, Med. Klin. **16**:225, 1920.

27. Fiore, T.: Alterazione delle vie lacrimali della congiuntiva e della cornea in conigli operati di zaffanemento completo di una fossa nasale, Arch. ital. di otol. **39**:530, 1928.

the conjunctival sac from the nose and vice versa. Suppurative dacryocystitis due to packing of the nose and also to pressure by a foreign body (a bean) in the nose has been reported by Kofler [21] and by Ruttin.[28]

The relationship of the turbinates to the lateral nasal wall is frequently altered by a marked septal deviation, a septal crest or a septal spur. This more or less compresses the inferior turbinate against the lateral nasal wall, producing obstruction of the nasolacrimal ostium. A number of authors, notably Bockstein,[29] Paterson [18] and Stenger,[26] have said that septal deviation is an important etiologic factor in disease of the lacrimal passages. Kofler [21] noted that the deviation was always on the affected side.

A large cyst or neoplasm of the antrum, especially in its anterior portion, or of the ethmoid sinus may in a similar manner compress the nasolacrimal ostium. Rarely does a neoplasm of the frontal sinus affect the lacrimal passages.

ACUTE INFLAMMATIONS OF THE NOSE

Acute as well as chronic inflammation of the nasal mucosa is often the cause of disease of the lacrimal passages. According to Lidström,[30] the acute nasal condition leads to the disease more frequently than does the chronic condition. An acute inflammatory condition of the nasal mucosa, especially in a severe form, such as that associated with diphtheria, measles and scarlatina, may quickly lead to disease in the lacrimal passages. These conditions on healing may leave scarring and synechia which not only involve the ostium but may involve the duct, causing partial or complete obstruction. Two cases of suppurative dacryocystitis have been reported by Kofler [21c]; in one the disease occurred in the course of measles, and in the other it was associated with diphtheria.

ATROPHIC PROCESSES IN THE NOSE

The frequent occurrence of stenosis of the lacrimal canal in association with atrophic processes, especially ozena, has been noted by

28. Ruttin, E.: Eitrige Rhinitis und Tränensäckblenorrhoe infolge eines Fremdkörpers in der Nase, Monatschr. f. Ohrenh. **50**:488, 1916.

29. Bockstein, F.: Ergebnisse von 180 endonasalen Dakryocystostomien, Zentralbl. f. d. ges. Ophth. **18**:7, 1927; Erfahrungen mit 150 endonasalen Dakryocystostomien, Ztschr. f. Hals-, Nasen- u. Ohrenh. **13**:223, 1926; Zur Frage über die endonasalen Fisteln bei Dakryocystostomie, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **9**:187, 1927.

30. Lidström, A. E.: Contribution to the Knowledge of the Incidence and Treatment of the Diseases of the Lacrimal Passages, Acta ophth. **1**:131, 1923.

Rollet and Bussy,[11b] Sondermann,[22] Bogendörfer[23] and Ferreri.[31] Dacryocystitis in the acute stage of ozena has been produced by nasal irrigation, which forced the infected secretions into the lacrimal passages (Ferreri[31]). Wojatschek[32] found that of 35 cases of dacryocystitis there was an atrophic process in the nose in 16 and marked ozena in many. Another writer, Heilmaier,[33] recorded 136 cases of atrophic rhinitis among 352 cases of dacryocystitis. Franceschetti[34] described a rare disease of the lacrimal sac which occurred in the course of atrophic rhinitis. It was demonstrated by having the patient blow with the nose closed, which resulted in a filling and distention of the previously emptied lacrimal sac.

MEMBRANOUS CLOSURE OF THE NASOLACRIMAL OSTIUM

Dacryocystitis caused by membranous closure of the nasal lacrimal passages in the course of inflammation of the nasal mucosa has been described by Wiener and Sauer.[35] Frequent acute inflammatory conditions by damaging the elastic fibers of the nasal mucosa lead to swelling of the membrane. The swelling in turn may cause constriction of the ostium or of the duct itself, especially where it is narrowed anatomically.

ABSCESS OF THE SEPTUM

Abscess of the lacrimal region following an abscess of the septum and abscess in the same region caused by a lettuce leaf driven into the nose have been noted by Bobone[36] and by Malgat.[37]

SINUSITIS

It is apparently generally believed that disease of the sinuses is an important contributing cause in dacryocystitis, since this etiologic factor is so frequently mentioned in the literature. The sinuses of the first series, especially the anterior ethmoid cells, because of their close ana-

31. Ferreri, G.: Endonasale Eröffnung des Saccus lacrimalis bei Ozaena, Klin. Monatsbl. f. Augenh. **79**:564, 1927.

32. Wojatschek, W. J.: Ueber die Entwicklung und Begrundung der Idee der intranasalen Eröffnung des Tränensackes, Zentralbl. f. d. ges. Ophth. **10**:514, 1923.

33. Heilmaier, O.: Beitrag zur Frage des Zusammenhanges von Augen- und Nasen- erkrankungen, Ztschr. f. Augenh. **2**:540, 1899.

34. Franceschetti, M. A.: Dacryocystite chronique consécutive à une sinusite maxillairé, Bull. et mém. Soc. franç. d'opht. **49**:27, 1935.

35. Wiener, M., and Sauer, W. E.: Dacryocystitis Caused by a Membranous Closure of the Nasal Duct, Arch. Ophth. **23**:487, 1914.

36. Bobone: Akuter nicht traumatischer Abscess des Septums mit sekundärem abscess der Tränenregion, Internat. Zentralbl. f. Ohrenh. **21**:254, 1914.

37. Malgat, J.: Corps étranger dans le canal lacrymal droit inférieur, Rec. d'opht. **12**:209, 1890.

tomic relationship to the lacrimal passages are not infrequently associated with one another pathologically. Kuhnt [17] in the examination of 100 patients with disease of the lacrimal sac found only 3 without nasal changes. Nine showed a variety of nasal diseases, 68 had positive sinus disease and 23 had probable sinusitis. Von Rhese [38] maintained that disease of the anterior ethmoid cells acts as a factor predisposing to chronic dacryocystitis. Brunzlow [39] stated that he could show positive involvement of the sinuses in 63.5 per cent of cases of dacryocystitis and presumptive involvement in 22 per cent and pointed out that ethmoiditis can often be ascertained only roentgenologically in such cases.

There are numerous reports of fistula from the antrum to the lacrimal sac, notably by Hammer,[40] Moscardi,[41] Mirow,[42] Guerra [43] and Sabbadini.[44] The association of phlegmonous dacryocystitis with fistula formation complicated by sinus disease has been reported by Hammer [40] and by Peters.[8] The latter showed that in 14 of 28 cases of phlegmonous dacryocystitis with fistula formation there was sinus disease and cautioned that one must always consider the possibility of empyema of the sinuses breaking into the lacrimal sac or its surroundings. Peters [8] further stated that in cases of dacryocystitis without fistula the rhinologic examination gave negative results.

In the examination of 110 patients with chronic dacryocystitis, I found that 55 per cent were afflicted with varying degrees of sinusitis. Suppuration of the anterior ethmoid cells was found to be more commonly associated with dacryocystitis than was suppuration of the other sinuses. The ethmoiditis may be a latent infection, as pointed out by Brunzlow [39] and by Paterson.[18] Fischer [45] found the nasal mucosa and ethmoid cells badly diseased in 19 of 32 cases of dacryocystitis. Similar findings have been noted by a number of other investigators,

38. von Rhese, cited by Meesmann, A.: Beziehungen der Tränensackleiden zur Nase und ihre Behandlung, Ztschr. f. Hals-, Nasen- u. Ohrenh. **27**:8, 1930.

39. Brunzlow: Pathologie und Therapie der Erkrankungen der Tränenableitungswege in ihren Beziehungen zur Rhinologie, Ztschr. f. Augenh. **43**:242, 1920.

40. Hammer: Ueber die Beziehungen der Phlegmonen und Fistelbildungen in der Gegend des Tränensackes, Inaug. Dissert., Rostock, 1904.

41. Moscardi, P.: Dacryoethmoiditis, Am. J. Ophth. **12**:44, 1929.

42. Mirow: Ueber Beziehungen der Phlegmonen und Fistelbildungen in der Gegend des Tränensackes zu den Nebenhöhlenerkrankungen der Nase, Inaug. Dissert., Rostock, 1921.

43. Guerra, P., cited by Franceschetti.[34]

44. Sabbadini, D.: Pansinusite con estrinsecazione orbitaria, Rev. oto-neuro-oftal. **9**:124, 1932.

45. Fischer, C. C.: Die Behandlung der Tränenwege durch das Totische Verfahren, Deutsche med. Wchnschr. **45**:814, 1919.

namely Fischer,[46] de Marzio,[47] Horgan,[48] Löwenstein,[49] Alexander[50] and Raia.[51]

Franceschetti[34] laid particular stress on suppuration of the maxillary sinus as an etiologic factor in chronic suppuration of the lacrimal sac.

Epiphora is not infrequently a prominent symptom of ethmoid mucoceles. Valude and Schiff-Wertheimer[52] commented on the complete absence of symptoms other than epiphora with these mucoceles. Two cases of epiphora associated with an ethmoid mucocele with complete cessation of the lacrimal discharge following opening of the mucocele have been reported by Charousek.[53] Kofler[21a] described a mucocele of the anterior ethmoid cells with an external fistula which simulated suppuration of the lacrimal sac. The roentgen examination showed that the lacrimal sac was not involved and did not communicate with the mucocele.

Unlike the authors cited, other observers, namely West,[54] Triebenstein,[55] Rochat[56] and Fenton,[57] have stated the belief that the main cause of disease of the lacrimal sac does not lie in the sinuses. While these writers admitted that ethmoiditis and dacryocystitis are occasionally associated, they said that ethmoid disease is not the most important etiologic factor. Bockstein[29] in 133 cases in which operation was per-

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46. Fischer, C. C.: Die Behandlung der Tränenwege von rhinologischen Standpunkt unter besonderer Berücksichtigung des Totischen Verfahrens, Ztschr. f. Augenh. **39**:1, 1918.

47. de Marzio, Q.: Sulle dacrio-etmoiditi, Riv. oto-neuro-oftal. **4**:715, 1927.

48. Horgan, J. B.: The Operation of Dacryocystorhinostomy: Its Indications and After-Treatment, J. Laryng. & Otol. **21**:225, 1916.

49. Löwenstein: Dakryocystorhinostomie nach Toti oder Eröffnung des Tränensackes von der Nase aus nach West-Polyak, Internat. Zentralbl. f. Laryng. **30**:474, 1914.

50. Alexander: Einfluss der Nebenhöhlenerkrankungen auf die Affektionen der Tränenwege, Ztschr. f. Laryng., Rhin. **11**:70, 1923.

51. Raia, V. L.: Toti's Operation for Dacryocystitis with Report of Sixteen Cases, Am. J. Ophth. **8**:547, 1923.

52. Valude and Schiff-Wertheimer: Mucocèle ethmoïdale simulant une dacryocystite, Presse méd. **36**:362, 1928.

53. Charousek, G.: Ueber paralakrimale und multiple Mucocelen, Monatschr. f. Ohrenh. **59**:129, 1925.

54. West, J. M.: The Intranasal Lacrimal Sac Operation, Arch. Ophth. **55**:351, 1926.

55. Triebenstein: Zur Behandlung der Tränensackeiterung, Klin. Monatsbl. f. Augenh. **74**:782, 1925.

56. Rochat, G. F., and Benjamins, C. E.: Experimente über die Tränenableitung, Arch. f. Ophth. **91**:66, 1916.

57. Fenton, R.: Indications, Contraindications and Preparation for Dacryocystorhinostomy, Ann. Otol., Rhin. & Laryng. **32**:67, 1923; Epithelioma of the Lacrimal Sac, J. A. M. A. **85**:1128 (Oct. 10) 1925.

formed could not ascertain the cause of the disease. He stated that in 600 patients who were referred for rhinologic examination because of epiphora the nasal findings were negative. Diggle [58] expressed more or less agreement with Bockstein. He examined 120 patients with disease of the lacrimal sac in order to establish a possible relationship between such disease and pathologic changes in the nose. He cited the sex and age of the patients, the duration of the symptoms, the anatomic configuration of the nose and the incidence of trauma and ethmoiditis. Most of his patients not only had no apparent nasal complaints but on close questioning denied having any nasal trouble.

CHRONIC INFILTRATIVE PROCESSES

Chronic infiltrative processes, such as tuberculosis, syphilis, scleroma and trachoma, frequently lead to disease of the lacrimal passages, according to Bogendörfer,[23] either by direct continuity or by metastasis. Axenfeld [59] and Meisner [60] stated the belief that tuberculosis of the lacrimal sac is secondary to primary tuberculosis in the nose. I have removed a lacrimal sac showing tuberculosis on histologic examination but unaccompanied with clinical evidence of tuberculosis of the nose. The sac may become involved by direct extension of the tuberculous process from its neighboring tissues, such as the nasal mucosa, the skin and the conjunctiva. It is also possible for the infection to come by way of the blood stream, according to Meisner.[60] He stated that for it to do so is not an unusual occurrence in children and in young adults. He remarked on the frequent association of tuberculosis of the lacrimal sac with that of the conjunctiva. Axenfeld [59] stated that tuberculosis of the lacrimal sac is more common than is generally believed, and Rollet [61] stated that it occurs in 8 per cent of cases. Hirschberg [62] reported 9 cases of intranasal tuberculosis, in 5 of which the condition was associated with disease of the eye and the lacrimal passages.

Endonasal fistulas, in the opinion of Schaeffer [4] and Elschnig,[63] may be congenital or may occur in the course of lacrimal disease which

58. Diggle, F. H.: Lacrimal Obstruction: Its Nasal Origin and Intranasal Treatment, Brit. M. J. **2**:933, 1927.

59. Axenfeld, T.: Die tuberculöse Erkrankung des Tränensacks, Med. Klin. **2**:158, 1906.

60. Meisner, W.: Tuberculose des Tränensackes, in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1930, vol. 3, p. 426.

61. Rollet: Die Tuberculose der Tränenwege, Klin. Monatsbl. f. Augenh. **49**: 11 and 113, 1911.

62. Hirschberg, cited by Meisner.[60]

63. Elschnig, A.: Angeborene Tränensackfistel, Klin. Monatsbl. f. Augenh. **44**: 57, 1906.

had its origin in the sac, in the nose or in the neighboring sinuses. Ploman [64] and von Szily [65] stated the belief that internal fistulas are often of tuberculous origin.

LUPUS

Lupus of the lacrimal sac associated with lupus of the nose has been noted by Hirschberg,[62] Davis,[66] Paterson and Fraser [67] and Heilmaier.[33] The commonest sites for the primary lesion of lupus are the vestibule, the septum and the anterior end of the inferior turbinate.

Stenosis of the nasolacrimal duct secondary to scrofulous infiltration of the nasal mucous membrane is cited by Kemler [68] and Malgat.[37]

SYPHILIS

Syphilis is mentioned as a frequent etiologic factor in dacryocystitis by Dewatripont,[69] Kemler [68] and Igersheimer.[70] Igersheimer stated that in children from 2 to 14 years of age hereditary syphilis accounts for 50 per cent of disease of the lacrimal passages, whereas such disease is uncommon with acquired syphilis and rare in newborn syphilitic infants.

In contradistinction to tuberculosis, syphilis not infrequently occurs as a primary disease of the lacrimal sac or of the skin overlying it. It may also extend from the inner canthus to involve the sac. In the tertiary stage it is mainly disease of the bone in the region of the lacrimal sac which leads to actual syphilitic involvement of the sac. Through obstruction of the lacrimal canal, syphilis may lead to non-syphilitic dacryocystitis. Gumma of the lacrimal sac has been reported by Galezowski.[71] In the opinion of Igersheimer,[70] the inflammation

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64. Ploman, K. G.: Beitrag zur Kenntnis der Fistula interna des Tränensackes, Klin. Monatsbl. f. Augenh. **81**:725, 1928.

65. von Szily, A.: Zur Pathologie der Tränenwege im Röntgenbild: V. Mitteilung, Klin. Monatsbl. f. Augenh. **64**:31, 1920.

66. Davis, E. D. D.: Diseases of the Lacrymal Apparatus of Nasal Origin, Tr. Ophth. Soc. U. Kingdom **49**:299, 1929.

67. Paterson, J. V., and Fraser, J. S.: Intranasal Dacryocystorhinostomy, Brit. J. Ophth. **3**:197, 1919.

68. Kemler, J. I.: Etiology of Lacrimal Disorders, Am. J. Ophth. **13**:610, 1930.

69. Dewatripont, L.: Beiträge zum Studium der bacteriologischen und histologischen Beziehungen zwischen der Erkrankungen der Nase und der Tränenwege, Monatschr. f. Ohrenh. **48**:865, 1914.

70. Igersheimer, J.: Ueber die Erkrankung der tränenabfuhrendere Wege bei hereditärer Lues, Klin. Monatsbl. f. Augenh. **52**:212, 1914.

71. Galezowski, J.: Atrophie du nerf optique consécutive à un phlegmon du sac lacrymal, Bull. Soc. d'opht. de Paris **19**:5, 1906; Tumeur lacrimale syphilitique, Rec. d'opht. **3**:179, 1876.

of the lacrimal sac is never itself syphilitic but is a secondary result of syphilis. The syphilitic involvement of the nasal mucosa or of the bony structure may produce stenosis of the lacrimal passages which leads to dacryocystitis. The involvement in congenital syphilis is frequently bilateral, since the stenosis is usually on both sides of the nose. Not infrequently, according to Igersheimer,[70] the patient suffers from syphilitic chorioretinitis or parenchymatous keratitis. He differentiated three groups of patients. In the first, disease of the nose could not be ascertained. He assumed that in these at some earlier period a closure of the nasal opening resulted in dacryocystitis. The second showed non-syphilitic changes in the nose but their causation was previous syphilitic involvement. In the third there were real syphilitic changes which could be recognized through the saddle nose deformity.

In my first series of 25 operations on lacrimal sacs I encountered 2 cases of external fistula of the lacrimal sac due to acquired syphilis.

PLASMOMA

Plasmoma of the lacrimal sac with plasmoma of the conjunctiva, a rather rare tumor or a form of chronic inflammation, has been reported by Verhoeff and Derby.[72] These writers expressed the opinion that the evidence points to an inflammatory origin of the condition. They stressed the clinical fact that it occurs frequently in conjunctivas showing evidence of existing or previous trachoma. The same authors quoted Marongiu, who stated that trachoma occurs in one third of the cases of plasmoma, a further indication of its chronic inflammatory causation.

TRACHOMA

Trachoma of the canaliculi with obliteration of the lumen at the entrance of the lacrimal sac has been described by Rubert,[73] Nicholls [74] and Cirincione.[75] Hoffmann [76] found 126 cases of dacryocystitis among 3,000 cases of trachoma of the conjunctiva (conjunctivitis granulosa). The trachomatous infiltration of the sac is characterized by a tendency to shrinking of the sac. Frank suppuration or dilation of the sac rarely

72. Verhoeff, F. H., and Derby, G. S.: Plasmona of the Lacrimal Sac, Arch. Ophth. **44**:252, 1915.

73. Rubert, J.: Zur Erkrankung der Tränenröhrchen insbesondere bei Trachom, Klin. Monatsbl. f. Augenh. **89**:193, 1932.

74. Nicholls, J. V. V., cited by MacCallan, A. F., and Sobhy, M.: Trachoma of the Lacrimal Sac, Tr. Ophth. Soc. U. Kingdom **42**:280, 1922.

75. Cirincione: Tracoma dei canalicoli lagrimali, Ann. di ottal. **19**:102, 1903.

76. Hoffmann, W. A.: Statistik über 3000 Fälle von Conjunctivitis granulosa, Inaug. Dissert., Königsberg, Karg & Manneck, 1906.

occurs, according to von Papolczy.[77] Not only does the infiltrative process affect the lacrimal passages, but in healing it may lead to fibrous constriction, according to the latter author, or even to closure of the nasolacrimal duct or its ostium.

LEUKEMIC INFILTRATION

Leukemic infiltration of the lacrimal sac has been observed by Stokes [78] and Stock [79] without evidence of leukemia in the blood.

TRAUMA

Trauma not infrequently is the underlying factor in disease of the lacrimal passages, and this may be either the result of injury to the lids in the region of the inner canthus or of operation in this region or the result of a fall, a blow, an injury by a firearm or a war injury. I operated on 3 patients who had obstructive dacryocystitis due to trauma. In 2 the condition was associated with fracture of the jaw and fracture of the nose; in 1 it was complicated with multiple fractures of the skull. Poirier [80] reported a case of dacryocystitis associated with fracture of the skull. On roentgen examination a fistula was found leading from the sac to the antrum.

Concerning operative trauma, injuries to the nasolacrimal canal and its outlet most often follow an operation on the lateral nasal wall; such injuries may result either in stenosis of the ostium or in complete closure of the canal. The procedures which particularly endanger the lacrimal canal and its nasal opening are removal of the anterior end of the lower turbinate near its attachment, as in the Denker, Caldwell-Luc and Sturmann-Canfield operations; removal of a malignant tumor or of a large cyst in the antrum after the Mikulicz-Krause method or its modification by Rheti, and the so-called Lautenschlager-Halle ozena operation.

NEOPLASMS, BENIGN AND MALIGNANT

Tumors of the lacrimal sac, both the benign and the malignant types, are not infrequently encountered. Cysts of the lacrimal sac, in the

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77. von Papolczy, F.: Beiträge zur Frage des Tränensacktrachomas, Klin. Monatsbl. f. Augenh. **92**:613, 1934.

78. Stokes, W. H., cited by Creutz, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1931, vol. 7, pt. 2, p. 347.

79. Stock, W.: Ueber Augenveränderungen bei Leukämie und Pseudo-Leukämie, Klin. Monatsbl. f. Augenh. **44**:328, 1906; cited by Meisner, W.: Pathologie der Tränenorgane, in Graefe, A., and Saemisch, E. T.: Handbuch der gesamten Augenheilkunde, ed. 2, Leipzig, Wilhelm Engelmann, 1925, vol. 9, chap. 15.

80. Poirier, G. H.: Toti-Mosher Operation, Arch. Otolaryng. **31**:549 (March) 1940.

opinion of Stock,[79] originate from the glands in the sac wall being caused by closure of their ducts, and also through diverticula of the mucous membrane. A good description of diverticulitis of the lacrimal sac from a histologic aspect was presented by Michail.[81]

Polyps of the sac may result, according to Stock,[79] from chronic inflammation of the sac; may follow trauma, probing, stricturotomy or incision of a phlegmon, and may also arise from an enlarged follicle.

Orzales [82] reported a case of polyp of the lacrimal sac and gave a brief review of similar cases reported by other writers. Heermann [83] described what appeared clinically to be papilloma of the lacrimal sac but on histologic examination proved to be fibroepithelioma.

Bilateral lymphoma of the lacrimal sac has been described by Sulzer and Duclos,[84] Weve [85] and Pascheff.[86] Stock [79] stated the belief that there occurs an infiltration of leukocytes into the tissues with local proliferation and multiplication of the cells in the perivascular spaces and contiguous tissues. Meller [87] ascribed the pathologic changes to stimulation with subsequent overgrowth of the preexisting lymphoid elements.

Secondary involvement of the lacrimal sac by direct extension of a malignant process from the nose or sinuses is more frequently observed than is primary involvement. Lymphoblastoma has been reported by Sédan, Astier and Caudière. [88] Primary carcinoma of the sac has been noted by Spratt,[89] and primary epithelioma has been described by Fenton.[57] I have treated a patient who suffered from melanotic sarcoma of the left ethmoid sinus. The tumor mass by direct extension involved the lacrimal sac and later spread to the orbit. I have under my observation an elderly woman who has carcinoma of the left antrum

81. Michail, D.: Sur la diverticulite kystique lacrymale, Arch. d'opht. **49**:384, 1932.

82. Orzales, F.: Un caso di polipo del saco lacrimale, Boll. d'ocul. **16**:1093, 1937.

83. Heermann: Die Verengerungen des Tränenkanals und deren Therapie, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **10**:679, 1927.

84. Sulzer, E., and Duclos, L.: Lymphome double du sac lacrymal suivi de lymphadénite généralisée sans leucémie, Rec. d'opht. **28**:353, 1906.

85. Weve, H.: Case of Lymphatic Tumor of the Lacrimal Sac, Nederl. tijdschr. v. geneesk. **72**:696, 1928.

86. Pascheff, C.: Symmetrische Tumoren und Adenoma Sacci lacrymalis, Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **46**:433, 1927.

87. Meller, J.: Diseases of the Lacrymal Apparatus, Tr. Ophth. Soc. U. Kingdom **49**:233, 1929.

88. Sédan, J.; Astier, A., and Caudière, M.: Lymphoblastome du sac lacrymal, Bull. et mém. Soc. franç. d'opht. **44**:249, 1931.

89. Spratt, C. N.: Cancer: Primary Carcinoma of Lacrimal Sac, Arch. Ophth. **18**:267 (Aug.) 1938.

with involvement of the lacrimal sac by direct extension of the malignant process. In giving her history, she stated that approximately eighteen months before she was aware of any trouble in the antrum she had marked epiphora of the left eye and noted a slight swelling over the left lacrimal region. This condition may have originated primarily in the sac or in the nasolacrimal duct and then spread to the antrum, since the epiphora was the only symptom noted by the patient long before she was aware of any trouble with the maxillary sinus.

IRRADIATION FIBROSIS

Postirradiation fibrosis, according to Kofler,[21c] after the use both of roentgen and of gamma rays, also may produce stenosis or complete closure of the lacrimal canal.

SWELLING DUE TO JEQUIRITOL

Seefelder [90] reported a rare form of dacryocystitis produced by the use of jequiritol (a 50 per cent solution of abrine [jequiritin] in sterile glycerin). He stated the belief that the dacryocystitis results from the marked swelling of the conjunctiva and spreads to involve the lacrimal sac.

HEREDITARY ANOMALIES

The hereditary or familial occurrence of disease of the lacrimal passages has been described by Schnyder,[91] and Groenouw [92] stated the belief that the cause of hereditary disease lies in hereditary anomalies of the facial skeleton. He stated that since the bony lacrimal canal is made up of the lacrimal bone, the ascending process of the maxilla and the lacrimal process of the inferior turbinate, it follows that the form, position and course of the lacrimal canal and likewise their anomalies are inherited. The disease of the lacrimal passages is contingent on a narrowing of the lumen of the lacrimal canal.

Long, narrow and tortuous lacrimal canals more easily lead to interference with canalization than the short, broad, straight canals with large lower orifices, such as are encountered in the Negro race, according to Santos-Fernández.[93] This observation serves to explain the infrequent occurrence of ailments of the lacrimal passages among

90. Seefelder, O.: Das Jequiritol, Klin. Monatsbl. f. Augenh. **43**:273, 1905.

91. Schnyder, W. F.: Ueber familiäres Vorkommen resp. die Vererbung von Erkrankung der Tränenwege, Ztschr. f. Augenh. **44**:257, 1920.

92. Groenouw: (*a*) cited by Schnyder [91]; (*b*) Die Augenentzündungen der Neugeborenen, Arch. f. Ophth. **52**:46, 1901.

93. Santos-Fernández, J.: Measurements of the Nasal Canal According to Race, Am. J. Ophth. **4**:32, 1921.

Negroes. The broad communication of the lacrimal duct with the nasal cavity does not predispose to infection, according to Campbell, Carter and Doub.[94]

OCULAR ORIGIN

The origin of disease of the lacrimal passages in the eye, although not as frequent as that in the nose, is nevertheless of some clinical significance. From the clinical point of view the route from the nose to the eye is considered by Martuscelli and Pirozzi [95] to be generally of greater importance than the reverse route. Campos [96] experimented with rabbits in order to establish this relationship. He completely exenterated the orbit in one rabbit; in another he destroyed the lacrimal passages by cauterization, and in a third he removed the eyelid. After an interval of two months the animals were killed and the tissues of the two sides of the nose were examined and compared. In no instance was there any difference between the tissues on the side operated on and those on the side not operated on.

Cilia not infrequently become lodged in the puncta, according to de Schweinitz,[97] and may also be lodged in the nasolacrimal duct. Gundersen [98] observed a case of obstruction in which a cast of the nasolacrimal duct was blown out in the middle of which was a cilium.

Uncorrected astigmatism and hypermetropia are mentioned by Savineau [99] as causes for dacryocystitis, especially in cases of low grade refractive anomalies and in cases of insufficiency of the internal rectus muscles. In such cases there are profuse secretion, stagnation of the tears in the lacrimal sac and decomposition of the secretions leading to irritation and inflammation of the lacrimal sac.

The older physicians [100] explained the greater frequency of chronic dacryocystitis in women on the basis of their using the lacrimal organs more frequently than men! Meller [87] and Schaeffer [4] stated the belief that the higher incidence among women is due to the peculiar

94. Campbell, D. M.; Carter, J. M., and Doub, H. P.: Roentgen Ray Studies of the Nasolacrimal Passageways, Arch. Ophth. **51**:462, 1922.

95. Martuscelli, G., and Pirozzi, F.: Il canale naso-lacrimale quale tramite delle infezioni da occhio a naso e viceversa, Arch. ital. di ottal. **33**:268, 1922; abstracted, Klin. Monatsbl. f. Augenh. **71**:259, 1923.

96. Campos, E.: Rhinologischer Beitrag zum Studium der Dakryocystorhinostomie, Zentralbl. f. d. ges. Ophth. **17**:54, 1927.

97. de Schweinitz, G. E.: Argyrosis of the Conjunctiva and Tear Sac, Tr. Am. Ophth. Soc. **10**:161, 1903.

98. Gundersen, T.: Personal communication to the author.

99. Savineau, cited by Meller.[87]

100. von Arlt, F.: Die Krankheiten des Auges, für praktische Aertze, Prague, F. A. Credner, 1854-1856. Fuchs, E.: Lehrbuch der Augenheilkunde, Leipzig, Franz Deuticke, 1889.

anatomy of their nasal bones, whereby the lumen of the lacrimal canal is narrower than in men.

In 110 patients with chronic dacryocystitis, including patients operated on and not operated on, I found the following conditions as possible etiologic factors:

	Cases
Chronic inflammation of the nasal mucosa (chronic rhinitis)	21
Chronic sinusitis, usually ethmoiditis, manifest or latent, occasionally associated with maxillary sinusitis	57
Trauma, associated with sinusitis (in 1 case, fracture of skull and fracture of the upper and lower jaws)	5
Deviation of septum, associated with purulent rhinitis	4
Atrophic rhinitis	3
Polyposis nasi	3
Tertiary syphilis, associated with sinusitis resulting in external fistula	2
Vasomotor rhinitis	2
Tuberculosis of sac; no clinical evidence of tuberculosis in nose	1
Osteoma of sac	1
Closure of nasal ostium of nasolacrimal duct in an infant	1
Congenital stenosis in a patient of 25	1
No evidence of nasal disease; causation uncertain	9
	110

BACTERIOLOGY

In a clinical and bacteriologic examination of 100 patients with dacryocystitis with ectasia of the sac, Rollet and Bussy [12b] observed infection with the pneumococcus in 60 per cent, with the staphylococcus in 20 per cent, with the streptococcus in 10 per cent and with the tubercle bacillus in 6 per cent. A mixed infection with the pneumococcus and the staphylococcus was found in 14 per cent; in 26 cases the bacteriologic examination gave negative results. Mucoceles were almost always sterile; secretions obtained at operations on the lacrimal sac (5 per cent of the cases) were bacteriologically not related to any specific organism. Escherichia coli in pure culture has been obtained in cases of various types of congenital dacryocystitis in very young infants by Francois,[101] Mercanti [102] and Stephenson.[103] A case of dacryocystitis due to Esch. coli in an infant suffering from enteritis has been reported by Bietti.[104] Esch. coli in pure culture has been isolated on a number of occasions from a phlegmon of the lacrimal sac by Groenouw,[92a] Mazet [105] and

101. Francois, J.: Le colibacille en pathologie oculaire, Arch. d'opht. **52**:424, 1935.

102. Mercanti, F.: Contributo all'etiologia della dacriocistite dei neonati, Ann. di ottal. **21**:133, 1893.

103. Stephenson, S.: A Preliminary Communication on Affections of the Tear-Passages in Newly-Born Children, M. Press & Circ. **119**:103, 1899.

104. Bietti, A.: Typische Blenorrhoea neonatorum durch Bacterium coli commune, Klin. Monatsbl. f. Augenh. **37**:311, 1899.

105. Mazet, C.: Sur l'empyème du sac lacrymal (Etude bactériologique et clinique), Thesis, Paris, no. 240, 1895.

Axenfeld.[106] Friedländer's pneumobacillus, which is closely related to the bacillus of ozena, has been isolated frequently from suppurative material from the lacrimal sac, according to Cuénod [107] and Terson and Gabrielidès.[108] Streptococcic infection of the lacrimal sac in the course of grip has been reported by Margaillan and Morenon,[109] who stated that it is more common than is generally believed. Infection of the lower canaliculus, with extension to the lacrimal sac, by Streptothrix fösteri and mycotic concretions have been described by McClanahan,[110] Talice [111] and Kemler.[68] A variety of fungi have been observed in association with infection of the canaliculi and the perilacrimal region by Fazakas,[112] Carsten [113] and Nagel.[114]

The usual chronic blenorrhea of the lacrimal sac, according to Dewatripont,[69] contains pneumococci, but in cases of the acute phlegmonous condition streptococci are usually observed, an indication of the nasal origin, since the lacrimal organs and the conjunctival sac normally do not contain streptococci. This, in the opinion of Dewatripont,[69] has led to the classification of dacryocystitis on a bacteriologic basis which suggests that in by far the greatest number of cases of infection of the lacrimal sac the condition is of nasal origin and that the natural route is through the lacrimal duct.

The following bacteriologic classification, based on thorough clinical and pathologic examinations, was suggested by Dewatripont. (He did not state the number of cases on which it was based.)

1. Pericystitis phlegmonosa
   (*a*) Streptococcic infection of nasal origin, mostly in adults.
   (*b*) Tuberculous infection, contingent on osteoperiostitis, usually in children.

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106. Axenfeld, T.: Ueber nicht gonorrhoische Blenorrhea der conjunctiva, Deutsche med. Wchnschr. **44**:698, 1898.

107. Cuénod, A.: Deux cas de dacryocystite ozéneuse, Arch. d'opht. **14**:495, 1894.

108. Terson, and Gabrielidès, A.: Recherche sur l'état microbienne de la conjonctive des ozéneux, Arch. d'opht. **14**:488, 1894.

109. Margaillan and Morenon: Infection streptococcique du sac lacrymal, Presse méd. **31**:546, 1923.

110. McClanahan, R.: Fungus Infection of the Lacrimal Canaliculi, Am. J. Ophth. **19**:418, 1936.

111. Talice, R. V.: A propos d'un cas de concrétions mycosiques primitives des canaux lacrymaux, Ann. de parasitol. **14**:169, 1936.

112. Fazakas, H.: Pilzbefunde in den Tränenkanalchen an den Augenlidern und den Lidrandern, Klin. Monatsbl. f. Augenh. **104**:49, 1940.

113. Carsten, P.: Pilzkonkremente im Tränenröhrchen, Ztschr. f. Augenh. **62**: 367, 1927.

114. Nagel, C. S. G.: Fungus Concretions in Lacrimal Canaliculus (Streptothricosis Actinomycosis), Am. J. Ophth. **3**:327, 1920.

2. Dacryocystitis tuberculosa, primary or secondary, with tuberculosis of the conjunctiva or the nose.
3. Dacryocystitis acuta (Streptococcus) of nasal origin, in the course of chronic dacryocystitis (Pneumococcus).
4. Dacryocystitis subacuta (Diplobacillus, Morax-Axenfeld) of nasal origin, occasionally due also to Pneumococcus.
5. Dacryocystitis chronica (Pneumococcus, Solamon-Fränkel) usually pure, sometimes due also to Staphylococcus, to Esch. coli, rarely to Bacillus pyocyaneus, to Gonococcus, to Bacillus xerosis subtilis, to Bacillus pyogenes foetidus, to Bacillus proteus vulgaris, to Week's bacillus, etc.
   (*a*) Without ectasia of the lacrimal sac (hypertrophic stage).
   (*b*) With marked ectasia of the lacrimal sac (atrophic stage).
6. Dacryocystitis ozaenosa (Löwenberg's diplococcus) of nasal origin; atrophy of the lacrimal sac.
7. Dacryocystitis syphilitica (Spirochaeta pallida) almost always secondary to nasal syphilis.
8. Dacryocystitis diphtheritica (Löffler), a frequent complication of nasal diphtheria.
9. Cystic ectasia of lacrimal sac (Staphylococcus, either in pure or in mixed culture).
10. Dacryocystitis trachomatosa, secondary to ocular involvement (suggested by Dr. Arnold Knapp).

One occasionally encounters a patient with chronic dacryocystitis who in spite of nasal disease recovers without any treatment. The spontaneous recovery may be attributed to a lysozyme normally present in the tears. This is an antibacterial enzyme widely distributed in nature and in the animal body. By means of it tears are able to dissolve in a few seconds at body temperature most of the air-borne bacteria, against which they therefore offer complete and immediate protection. Even virulent organisms, such as Staphylococcus, Streptococcus, Meningococcus, Gonococcus, Bacillus anthracis, Bacillus tuberculosis and Vibrio cholerae, are destroyed in a few hours by exposure to normal human tears at body temperature. Organisms of the diphtheroid group are, however, resistant (Wolff,[115]).

REFLEX EPIPHORA

Meller [87] stated that the majority of opthalmologists err in assuming epiphora to be entirely associated with narrowing of the lacrimal passages. He asserted that "though there may be no striking or essential changes in the nose, the epiphora may still originate here." He continued:

We have for years, in non-obstructive epiphora, systematically examined the nose by means of a probe (Weleminsky) and ascertained that by touching certain

115. Wolff, E.: A Pathology of the Eye, Philadelphia, P. Blakiston's Son & Co., 1934.

parts, especially the inferior end of the middle turbinate and the tuberculum septi, we could inaugurate profuse lacrimal secretion. Here the mucous membrane is not entirely normal, but is either hypertrophic or edematous or in certain cases pale and thin, but permeated by a large number of dilated vessels. Furthermore, a striking phenomenon was observed in that these areas reddened on cocainization.

Szily [65] described hyperesthetic zones which apparently resulted from the influence of circulatory disturbances and by pathologic reflex irritability increased the secretion of tears, with the result that epiphora occurred. If for such disturbances the usual method of scarification is employed, the increased reflex irritability disappears in from one to three days and with it the epiphora. A cure of lacrimation of long standing by this method of treatment has been reported by Bogendörfer.[23]

Hypersecretion of tears and epiphora may be produced on a basis of nasofacial reflexes. The process is in a manner a physiologic sympathetic reaction of the conjunctival mucous membrane to irritation of the endonasal mucosa, according to Bogendörfer.[23] Similarly, Weill, Baillard and Phillips [116] associated rhinorrhea and epiphora and said that both manifestations are vagotonic, whether influenced by tuberculous toxins or influenced by pressure of tuberculous glands on the vagus. Weiss and his associates [117] described lacrimation in patients suffering from a hyperactive carotid sinus reflex.

Savin [118] described 3 patients who had profuse lacrimation while eating. All had a history of facial paralysis with more or less incomplete recovery. He quoted Bogorad,[119] who aptly named this phenomenon "crocodile tears," after the hypocritical tears which legend said these reptiles shed before devouring their victims, as reported in the "Travels" of Sir John Mandeville, published about 1400. Tumarkin [120] reported a series of 13 cases, and he stated that such lacrimation can be explained on the basis of Bell's palsy and called it a form of synkinesia. Russin [121] reported 2 cases of excessive lacrimation during the partaking of acid, salty or bitter foods. In both cases there was a history of trauma to the head and face with residual incomplete facial paralysis.

116. Weill, Baillard, and Phillips, cited by Buzoianu, G.: Epiphora chronique d'origine nasale, Rev. de laryng. **57**:224, 1936.

117. Weiss, S.; Capps, R. B.; Ferris, E. B., Jr., and Munro, D.: Syncope and Convulsions Due to a Hyperactive Carotid Sinus Reflex, Arch. Int. Med. **58**:407 (Sept.) 1936.

118. Savin, L. H.: Three Cases Showing Crocodile Tears After Facial Paralysis, Brit. J. Ophth. **32**:479, 1939.

119. Bogorad, F. A.: Syndrome of Crocodile Tears, Vrach. delo **11**:1328, 1928.

120. Tumarkin, I. A.: Syndrome of Crocodile Tears, Lancet **1**:26, 1936.

121. Russin, L. A.: Paroxysmal Lacrimation, J. A. M. A. **113**:2310 (Dec. 23) 1939.

Schirmer [122] stated that epiphora in association with complete facial paralysis is contingent on the complete absence of blinking; drainage of tears in immobile or immovable lids does not occur. The basis of the absence of blinking, according to the same authors, is the paralysis of the orbicularis oculi muscle.

SUMMARY AND CONCLUSIONS

A review of the literature on the etiology of dacryocystitis and epiphora is presented. It leads to the following conclusions:

1. Dacryocystitis is contingent on stenosis of the nasolacrimal duct, either congenital or acquired, plus a secondary infection.

2. The opinion of the majority of the authors cited is that the etiologic factor is usually to be found in the nose in the form of an acute or chronic inflammation or in disease of the sinuses.

3. Trauma, physical or surgical, and infectious diseases of the nose may also play a part in the causation of dacryocystitis.

4. Specific chronic inflammatory disease, such as tuberculosis and syphilis, not infrequently causes dacryocystitis.

5. Benign or malignant neoplasms, either by primary involvement or by metastases, occasionally involve the lacrimal drainage apparatus.

6. The disease less frequently arises from the eye.

7. Epiphora may result from reflex irritation or from stimulation of the facial or the vagus nerve or of sympathetic nerves.

8. A thorough rhinologic examination is indicated in all cases of disease of the lacrimal passages.

9. In a number of cases the cause of dacryocystitis cannot be ascertained.

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122. Schirmer, O.: Studien zur Physiologie und Pathologie der Tränenabsonderung, Arch. f. Ophth. **56**:211, 1903.

Correspondence

THE AXIS IN ASTIGMATISM

To the Editor:—The article by Dr. Wendell L. Hughes in the November issue of the ARCHIVES on the change of the cylinder axis for near vision (ARCH. OPHTH. **26:** 742 [Nov.] 1941) is especially interesting because it refutes a current belief that ophthalmologists are interested primarily in surgery and medicine and pay but little attention to the refinements of refraction. One gets such an impression because so few papers on refractive problems are presented at scientific ophthalmologic meetings. The hypothesis for such changes given in the paper is, I think, hardly probable.

In line with the Helmholtz-Fincham theory of accommodation a weakness of the zonular fibers at some place in the circumference would leave the corresponding portion of the capsule under diminished tension. This would allow the corresponding portion of the lens to bulge out a little more, an effect that would be especially manifest in the unaccommodated eye. During accommodation the weakness of some zonular fibers would be of less import in the general relaxation of the whole zonule. Besides, such a mechanism would if anything produce slight but irregular refractive changes, hardly a definite change of axis in the same power cylinder.

A more plausible hypothesis is that the action of the extrinsic muscles in near vision slightly changes the curves of the cornea. But a slight change in the curves of the cornea would be required to produce slight changes in the direction of the astigmatic meridians when the eye changes from looking straight ahead to looking down and in (converging). One can sometimes study the changes in the corneal curves with the ophthalmometer before and after the eye is placed under muscular tension from the extrinsic muscles, not the ciliary muscles. Such corneal changes would be especially likely to appear in corneas which are more yielding because of lessened vitality and resistance. The report of Dr. Hughes's cases partly bears this out. In his first fully documented case corneal ulceration developed. Patient 6 had suffered from corneal ulcerations and patient 7 had a pseudoconical cornea. Another contributing element in partial confirmation of this hypothesis is the fact that patients 1 and 2, who had no extraneous complications, such as squint or injury, showed exophoria for near vision; patient 1, 30 prism diopters, and patient 2, 6 prism diopters. It seems reasonable to assume that more effort and greater muscular tension are required to maintain convergence in the presence of exophoria. Increased muscular tension would naturally have more effect on a yielding cornea.

That the normal cornea also yields to pressure and tension can be seen from the application of contact lenses. On applying such lenses one sees not infrequently the appearance of astigmatism in the cornea because of slight scleral pressure. The eye with a well centered, well fitting

contact lens may show no astigmatism whatever. But with another contact lens, one which exerts some pressure somewhere, astigmatism is at once evident. Similar corneal changes may be seen on ocular rotations with a contact lens.

A few points in cases 1 and 2 call for comment. In case 1 four examinations within one year showed results, tabulated for easy analysis, as follows:

Right eye, distance vision:	(1) + 1.00 D. cyl., axis 155
	(2) + 1.00 D. cyl., axis 155
	(3) + 1.00 D. cyl., axis 155
1 year later	(4) + 1.00 D. cyl., axis 148
Right eye, near vision:	(1) + 1.00 D. cyl., axis 135
	(2) + 1.00 D. cyl., axis 118
	(3) + 1.00 D. cyl., axis 120
1 year later	(4) + 1.00 D. cyl., axis 130
Left eye, distance vision:	(1) + 0.75 D. cyl., axis 15
	(2) + 0.75 D. cyl., axis 15
	(3) + 0.75 D. cyl., axis 10
1 year later	(4) + 0.25 D. cyl., axis 35
Left eye, near vision:	(1) + 0.75 D. cyl., axis 15
	(2) + 0.75 D. cyl., axis 180
	(3) + 0.75 D. cyl., axis 180
1 year later	(4) + 0.25 D. cyl., axis 75

Not only was there a change in the cylinder axis for distance and for near vision at the same examination but there were changes, some slight and some considerable, in the cylinder axis for distance and for near vision at different examinations. Thus the right cylinder axis for distance vision was 155 degrees at one time and 148 degrees at another. The right cylinder axis for near vision varied between 118 and 135 degrees. The left cylinder axis for distance vision varied between 10 and 35 degrees, while for near vision it varied between 180 and 75 degrees.

Similar changes, both in axis and in strength of cylinder found at different examinations for distance vision, were also recorded in case 2. Omitting the spherical correction, one finds at three examinations:

Right eye, distance vision:	(1) + 0.25 D. cyl., axis 70
2 years later	(2) + 0.62 D. cyl., axis 70
6 years later	(3) + 0.62 D. cyl., axis 15
	(for near vision, + 0.62 D. cyl., axis 75
Left eye, distance vision:	(1) + 0.50 D. cyl., axis 92
2 years later	(2) + 0.75 D. cyl., axis 90
6 years later	(3) + 0.25 D. cyl., axis 90

The hypothesis that muscular tension associated with ocular depression and convergence may change the cylinder axis for near vision from that for distance vision can account in a way for the different axes found for near vision at different times. The degree of muscular tension is not likely to be the same at different times, and different degrees of tension would produce slightly different effects. This would hardly account, however, for the change of axis in the lenses for distance vision.

Another point worth noting is the change in the strength of the cylinder. In case 1 the cylinder for the left eye changed after a lapse of one year from + 0.75 D. to + 0.25 D. Possibly a yielding cornea tended to assume a more nearly spherical shape in response to the funiform internal hydrostatic pressure. But this suggestion would hardly hold in case 2, in which there is no mention of corneal weakness. In this case the cylinder changed for distance vision for the right eye from + 0.25 D. to + 0.62 D. and for the left eye from + 0.50 D. to + 0.75 D. and then to +0.25 D. This problem is not touched on in the article and is mentioned here only because it is closely correlated to the condition described in the article.

As a final word it may be said that even providing the patient with a different cylinder axis for far and for near vision will not provide him with a perfect correction for all distances. The axis for intermediate distances, between 6 meters and 35 cm., is most likely different from both the axis for 6 meters and the axis for 35 cm. Therefore, though giving the best correction, and one should give no less, one must realize that a stationary fixed power lens before a mobile living eye whose visual requirements are constantly varying in ordinary use is but an approximation.

JOSEPH I. PASCAL, M.D., New York.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Anterior Chamber

CONCERNING THE CHAMBER ANGLE: I. GONIOSCOPY. H. S. SUGAR, Am. J. Ophth. **23:** 853 (Aug.) 1940.

From his studies of the angle of the anterior chamber Sugar comes to the following conclusions:

"1. The normal angle of the anterior chamber has definitely recognizable characteristics, depending to some extent on the color of the iris. When trabecular pigment is present, its source is always the pigment epithelium of the iris. Its relation to glaucoma is still an unclarified point.

"2. Gonioscopy is an important adjunct to thorough ophthalmic examination. It is of particular value in studying anomalies, neoplasms, cysts, and the results of trauma involving the angle. Perhaps most important is its use in studying postoperative glaucoma, particularly in determining the reasons for surgical failure.

"3. Peripheral anterior synechiae are present in a large percentage of eyes operated upon to relieve glaucoma. These add to the embarrassment of previous drainage channels but are significant only when the new surgically formed channels are inadequate. They must be considered in contemplating secondary surgery.

"4. Peripheral anterior synechiae are not present in early and even moderately advanced compensated cases of glaucoma which have never been incompensated at any time. They occur only late in the glaucomatous process, probably beginning with edema of the ciliary body during an episode of incompensation."

W. S. REESE.

Bacteriology and Serology

EXPERIMENTAL ANAPHYLAXIS AND ALLERGY. R. ARGAÑARAZ, Arch. de oftal. de Buenos Aires **14:** 943 (Nov.) 1939.

Argañaraz reports a series of experiments in which anaphylactic inflammation in the conjunctiva and the lids was produced by instilling into the eyes of previously sensitized rabbits a few drops of horse serum. The results are compared with negative results in nonsensitized animals.

The author further records a slight primary reaction after the inoculation of the cornea of a nonsensitized rabbit with a couple of drops of horse serum, followed by a violent reaction fourteen days later after a subcutaneous injection of 2 cc. of horse serum (sensitization having been produced by the primary inoculation). A third injection after another fourteen days was followed by a more marked inflammatory reaction not only in the inoculated eye but in the other eye. This con-

firmed Schick and Riehm's and Igersheimer's views on inflammation in tissues such as the cornea and the uvea through the passage into the blood of albuminoid ferments which sensitize similar tissues in the other eye. If the animal is sensitized before the corneal inoculation, the reaction after the inoculation is most intense.

From these experiments, conclusions are drawn on the allergic nature of the ocular reaction to tuberculin, of the ocular symptoms of hay fever, of idiosyncrasies to certain drugs, of vernal conjunctivitis, of granulations in various conjunctival disturbances, of parenchymatous keratitis (the spirochete in the syphilitic form acting as the sensitizing allergen), of sympathetic ophthalmia, of endophthalmitis phacoanaphylactica and of phlyctenular and nodular infiltration in so-called scrofulous ophthalmia.

C. E. FINLAY.

Biochemistry

THE BIOCHEMISTRY OF THE LENS: A RÉSUMÉ. J. E. LEBENSOHN, Am. J. Ophth. **23:** 784 (July) 1940.

Lebensohn discusses the constituents, growth and metabolism of the lens; the capsule; changes in cataract, and experimental cataract. He then presents some therapeutic conclusions as to the management of cataract and suggests that the health of the lens depends on the state of the body.

W. S. REESE.

THE MUCOPOLYSACCHARIDE ACID OF THE CORNEA AND ITS ENZYMATIC HYDROLYSIS. K. MEYER AND E. CHAFFEE, Am. J. Ophth. **23:** 1320 (Dec.) 1940.

From cattle cornea Meyer and Chaffee isolated a polysaccharide, which they characterize as a sulfuric acid ester of hyaluronic acid, which to their knowledge occurs only in the cornea. They speculate as to this polysaccharide's being connected with corneal transparency and absence of corneal blood vessels.

W. S. REESE.

Cornea and Sclera

THERAPEUTIC CORNEAL TRANSPLANTATION FOR KERATITIS. V. SKORODINSKAYA, Vestnik oftal. **17:** 699, 1940.

The conserved cornea from the cadaver has been used for therapeutic transplantation in 68 cases of keratitis since 1936 in the Institute of Experimental Ophthalmology. Thirty-nine cases observed during one year are analyzed. Thirteen were of syphilitic interstitial keratitis. The keratitis in 12 was tuberculous, in 1 sclerosing in 3 herpetic, in 2 filamentous and in 5 trachomatous. In 2 the condition was keratitis rosacea and in 1 keratitis after trauma. The best results were obtained in the treatment of syphilitic keratitis, particularly in the period of severe inflammation. The vision was improved in 32 cases; in 3 cases there was no improvement, and in 4 cases (2 of tuberculous and 2 of filamentous keratitis) the process recurred. Antisyphilitic therapy was begun in the cases of syphilitic keratitis after the transplantation. These were the characteristic features of the postoperative period: (1) cessation of pain in two to three days after the operation; (2) aggrava-

tion of the inflammation from three to seven days (in trachoma from two to three weeks) after the operation; (3) disappearance of photophobia and ciliary injection in four to ten days, with clearing of the cornea ensuing (in trachoma in three to four weeks), and in trachoma improvement of the conjunctiva. The prolonged therapeutic influence of the conserved corneal tissue on the inflammatory process is evidently the important factor for the therapeutic value of corneal transplantation in the treatment of keratitis.

O. SITCHEVSKA.

FETAL KERATOMALACIA. H. D. BOUMAN AND S. VAN CREVELD, Maandschr. v. kindergeneesk. **9:** 343 (June) 1940.

Bouman and van Creveld observed a mother aged 16 who during the first six months of pregnancy had had an inadequate diet, particularly with regard to vitamins. She had eaten mostly white bread and a margarine to which no vitamins had been added. She had had no milk or eggs and only once a week lean meat and greens. She gave birth to a child with such severe ocular defects that complete blindness will be the result. The authors regard these congenital defects as a result of fetal keratomalacia.

J. A. M. A. (W. ZENTMAYER).

General

BINOCULAR ANOMALIES AND READING ABILITY. B. CLARK, Am. J. Ophth. **23:** 885 (Aug.) 1940.

From a study of the literature Clark concludes that there is little difference between good and poor readers in the number of visual defects in general and of binocular defects in particular. He reviews the different phases of reading disability and the problems involved that require study and elucidation.

W. S. REESE.

OCULAR SIGNS AS AN AID IN DISTINGUISHING BETWEEN IDENTICAL AND NONIDENTICAL TWINS. G. JANCKE, Arch. f. Ophth. **142:** 113, 1940.

The ocular characteristics which are of value in establishing that twins are identical are the general appearance of the eyebrows and lids and the color and structure of the iris. Detailed observations on 144 pairs of twins are reported. The author concludes that "from ocular signs alone an experienced observer can determine with the greatest possible accuracy whether twins are identical."

P. C. KRONFELD.

General Diseases

HYPERURICEMIA AND INFLAMMATIONS OF THE EYE. H. C. KLUEVER, Am. J. Ophth. **23:** 867 (Aug.) 1940.

Kluever reports 3 cases of iritis in which reduction of a high blood uric acid content was followed by improvement, the rate of recovery apparently coinciding with the rate of reduction. He concludes that the

infrequency with which gout is being associated with ocular inflammations is misleading.

W. S. REESE.

CROUZON'S DISEASE. J. A. GALLINO and J. A. ONETO, Arch. de oftal. de Buenos Aires **14:** 1010 (Dec.) 1939.

A case is reported of Crouzon's disease with cranial deformity, exophthalmos, atrophy of the optic nerve, divergent strabismus and maxillofacial deformity. The text is illustrated with photographs and roentgenograms. The literature is reviewed and statistics given as to the frequency of different elements in the deformity.

The authors distinguish three stages: (1) dysostosis commencing shortly after birth, with infiltration of the cranial sutures and the development of synostosis; (2) the appearance of compensatory ectasia of the cranial contents; (3) cranial compression and the dysostosis syndrome.

The atrophy of the optic nerve has been explained by papillary stasis and by compression in the optic canal.

The exophthalmos is due to reduction in the depth of the orbit.

C. E. FINLAY.

Glaucoma

BLOOD DIFFERENTIAL COUNT IN CHRONIC GLAUCOMA. E. M. BLAKE and J. C. LEONARD, Am. J. Ophth. **23:** 907 (Aug.) 1940.

Blake and Leonard give the following summary of their work on the differential count in glaucoma.

"1. A differential count was made on the blood of 100 consecutive unselected glaucomatous patients. 2. These blood films were stained with Wright's stain and a differential count was made by one individual. 3. The monocyte percentage ranged from 2 to 15 per cent, 94 per cent of the patients having monocyte counts within the normal range of 2 to 10 per cent. 4. The monocyte count is of no value in the diagnosis of glaucoma."

W. S. REESE.

ACTION OF PILOCARPINE, HOMATROPINE AND COFFEE ON THE INTRAOCULAR TENSION OF THE NORMAL EYE EVALUATED FOR THE DIAGNOSIS OF LATENT GLAUCOMA. I. GILDE, Klin. Monatsbl. f. Augenh. **101:** 586 (Oct.) 1938.

The author's research on the effect of pilocarpine, homatropine and coffee in glaucomatous eyes was based on the lability of tension, a predominant symptom of glaucoma. Homatropine caused a slight increase of the intraocular tension in 30 normal eyes. The maximum increase occurred after one to one and one-half hours, but the normal borderline was not exceeded. A slight increase in the intraocular tension after instillation of pilocarpine in normal eyes was followed by a moderate decrease. The curves showed a typical course in each case, although the increase and the decrease in tension varied individually. Coffee also produced a slight increase in the intraocular tension. The tests showed that the intraocular tension was influenced qualitatively in a

similar manner in normal eyes and in glaucomatous eyes. The diagnosis of latent glaucoma therefore can be made only in cases in which the increase in the intraocular tension exceeds the physiologic borderline.

K. L. STOLL.

Ocular Muscles

DYSFUNCTION IN THE VERTICAL MOVEMENTS OF THE EYES (OBLIQUE SQUINT AND OCULAR TORTICOLLIS). J. MALBRAN, Arch. de oftal. de Buenos Aires **15:** 65 (Feb.) 1940.

After acceptance of Bielschowsky's classification of dysfunctions of the vertical eye muscles, the author discusses the Marquez-Bailliart and the Franceschetti diagrams of their action, concluding that an eye muscle never acts singly. He then takes up the action of the vertical muscles in oblique positions of the head.

In connection with the relative frequency of these dysfunctions, Malbran agrees with Bielschowsky that paralysis of the superior oblique muscle predominates, attributing the increase in relative incidence during the last twenty-five years from 10 to 20 per cent to the increase in use of the radical Killian operation on the frontal sinus. As to other etiologic factors, in 15 per cent of cases the dysfunction is of traumatic origin. That due to syphilis has decreased from 55 to 25 per cent. That due to congenital anomalies or to epidemic encephalitis has a relative incidence of 14 per cent. In the examination of patients the author follows a routine:

1. He determines the position of the image of the paralyzed eye.

2. In studying the diplopia he determines whether the increase in divergence is (*a*) toward the right or the left or (*b*) down or up. (He refers to the necessity of studying both the lateral and the vertical deviation in adduction and in abduction, the lateral deviation being influenced by a preexisting heterophoria.)

3. He determines the inclination of the false image (in doing which, like Bielschowsky, he uses a horizontal line).

4. He studies the inclination of the head in the normal position and in vertical movements.

The author next takes up hyperfunction of the inferior oblique muscle, directing attention to points of differentiation between this and paresis of the superior rectus muscle.

In relation to treatment, he takes up successively advancement of the paretic muscle, tenotomy of the antagonist, advancement of the associated muscle of the same eye, transference of function to another muscle (along the lines indicated by Jackson) and tenotomy of the associated muscle of the sound eye, indicated chiefly when there is hyperfunction of the inferior oblique muscle.

C. E. FINLAY.

ESOTROPIA IN MYOPES. B. SZINEGH, Arch. f. Ophth. **142:** 176, 1940.

The author considers the occurrence of esotropia in myopes a pure coincidence, the myopia having been inherited from one parent and the tendency toward esotropia from the other parent. Three cases which seem to corroborate this view are reported.

P. C. KRONFELD.

The Pupil

TONIC PUPIL. E. ADROGUÉ and A. CAMMAROTA, Arch. de oftal. de Buenos Aires **14:** 863 (Sept.) 1939.

A case is reported of tonic pupil in a patient with a persistent pupillary contraction which had followed an accommodative convergent reaction. This syndrome was first described by Strasburger and Saenger in 1902.

The negative results of neurologic investigation are in keeping with the vagueness of the opinions expressed in connection with this pupillary syndrome and its cause. The variations in reported cases are discussed without the authors' reaching definite conclusions. In the present case the history is opposed to the anomaly's being considered congenital.

C. E. FINLAY.

PUPILLATONIA AND SYPHILIS. S. S. GABARD, Arch. de oftal. de Buenos Aires **14:** 1006 (Dec.) 1939.

Gabard refers to a paper by Alajouanine and Morax on pupillatonia in Adie's syndrome in 100 cases in which syphilis was the most probable cause. He then reports on pupillatonia in a woman who had been treated for syphilitic paraplegia for fourteen years and at the time he saw her still showed weakness in the legs, absence of the osteotendinous reflexes, the Romberg sign and unilateral pupillatonia on the right. The right pupil, which at one time was totally immobile, was dilated and showed a delayed reaction to light and in accommodation. The range of accommodation was higher in the tonic pupil. The action of collyriums on tonic pupil was rapid and surpassed that on the other eye.

The author agrees with Alajouanine and Morax in considering pupillatonia a regressive stage of a more advanced lesion.

C. E. FINLAY.

Physiology

DARK ADAPTATION AND DIETARY DEFICIENCY IN VITAMIN A. L. F. STEFFENS, H. L. BAIR and C. SHEARD, Am. J. Ophth. **23:** 1325 (Dec.) 1940.

After experiments on human being Steffens, Bair and Sheard come to the following conclusions:

"1. In three normal adult subjects, the thresholds of light brightness and the courses of dark adaptation of the macular areas and of regions 10 degrees above the macula were not affected significantly (less than 0.5 log unit) during the course of a dietary regimen very low in vitamin-A content (100 to 300 international units daily) for periods of 42, 160 and 190 days, respectively.

"2. The experimental results were checked and corroborated by tests made with different intensities of, and exposure to, the light-adapting field (160 to 1,500 foot-candles) and with retinal stimulus areas of 0.33, 1, and 2 degrees, respectively. Other types of apparatus for the photometric measurements of visual adaptation gave comparable data.

"3. These results show that, in certain normal adults, considerable periods of deficiency in the intake of vitamin A may be maintained without producing any significant changes in rod or cone sensitivity.

"4. Microscopic examinations of the skin of one of the subjects, who had been on a diet very low in content of vitamin A for 190 days, showed the presence of changes which, it is believed, generally occur in late stages of A avitaminosis. Restoration to a normal cutaneous condition, except for keratotic plugs in the hair follicles, occurred in about three weeks on normal diets supplemented with a fairly large (80,000 units) daily intake of vitamin A.

"5. Measurements on dark adaptation have been made in a few clinical cases of persons reporting restricted and low vitamin diets for prolonged periods and in conditions of follicular hyperkeratosis. In general, in these conditions, threshold levels are above normal; high vitamin diets cause restoration to the normal range, although there are marked differences in the periods of time required."

W. S. REESE.

Retina and Optic Nerve

A STUDY OF THE INTERRELATIONSHIP OF RETINAL AND SYSTEMIC ARTERIAL PRESSURES AND INTRAOCULAR TENSION IN NORMAL AND SYPHILITIC PATIENTS. E. F. CONSTANTINE, Am. J. Ophth. **23:** 436 (April) 1940.

The author gives the following summary:

"A study of the intraocular tension, the peripheral systemic systolic and diastolic blood pressures in (a) 38 normal individuals, (b) 8 patients with central-nervous-system syphilis, but without optic atrophy, (c) 16 patients with central-nervous-system syphilis with primary optic atrophy; and (d) 5 patients with central-nervous-system syphilis who had an ophthalmic reaction from tryparsamide therapy, gives no support to the theory of Lauber and Sobanski on the pathogenesis of optic atrophy. On the contrary, the results are in direct contradiction to their theory. No peripheral vascular or retinal hypotension was observed in patients with central-nervous-system syphilis, either with or without optic atrophy. The differential between the retinal diastolic pressure and the intraocular pressure was not reduced in patients with optic atrophy. On the contrary, it was higher in these patients than in normal controls."

W. S. REESE.

AN EXPOSITION OF SOME ROUND MACULAR LESIONS. A. J. BEDELL, Am. J. Ophth. **23:** 520 (May) 1940.

After describing 15 cases of various round macular lesions and showing their photographs Bedell presents the following conclusions.

"Early changes in the macula are best seen with the aid of an arc lamp.

"Serial photographs supply the only scientifically accurate method of recording fundus changes.

"Before an eye with a macular lesion is enucleated, photographs should be taken.

"A complete understanding of the macular-degeneration cycle is necessary.

"By means of serial photographs many suspected malignant lesions have been proved to be hemorrhagic, and the globes have been preserved."

W. S. REESE.

AMAUROTIC IDIOCY AND RELATED CONDITIONS. A. HAGEDORN, Am. J. Ophth. **23:** 735 (July) 1940.

Hagedorn discusses amaurotic family idiocy and certain diseases associated with abnormal lipoid metabolism, namely Niemann-Pick, Gaucher and Schüller-Christian disease, mainly from the standpoint of pathology. He considers these related conditions, pointing out that Tay's sign has been noted in 6 cases of Niemann-Pick disease.

W. S. REESE.

POST-PARTUM RETINAL ARTERIAL OBSTRUCTION ASSOCIATED WITH HEMIPLEGIA. A. M. WRIGHT THOMSON, Brit. M. J. **1:** 387 (March 9) 1940.

In the seventh month of pregnancy a woman aged 33 had a uterine hemorrhage which was moderate in amount and did not lead to collapse. She recovered, but on the seventh day, when she was about to rise from bed, she felt faint and closed her eyes for five minutes. When she reopened her eyes she found that the left eye was blind and that she had lost the power of her right arm and leg. The hemiplegia was transient, and the patient recovered from it in two days, but the loss of vision persisted. The vision was reduced to perception of hand movements in the temporal half of the field, and the ophthalmic picture was that of closure of the central retinal artery. The patient did not recover vision except in the peripheral area; the central area remained blind, and atrophy of the optic nerve developed.

The author thinks that these symptoms may have been due to a thrombosis of the internal carotid artery which led to necrosis of the pituitary gland. This is suggested by the presence of some of the symptoms of pituitary disturbance, such as abnormal feelings of coldness and the absence of mammary reaction. The fact that the hemiplegia was only transient points to arterial spasm as the cause. However, the retina apparently was permanently damaged; this fact does not exclude spasm altogether, but it makes an organic obstruction seem likely as the cause of the interruption.

ARNOLD KNAPP.

FUCHS'S NEURITIS PAPULOSA. P. KURPLAT, Arch. de oftal. de Buenos Aires **14:** 859 (Sept.) 1939.

A case is reported of the condition described by Fuchs under the name neuritis papulosa. The patient was a Brazilian 39 years of age. The disease is differentiated from epipapillary membrane (a congenital lesion), from choroiditis and from retinitis proliferans.

C. E. FINLAY.

CEREBRAL AND RETINAL ANGIOMA WITH CAPILLARY MALFORMATION IN THE SKIN. C. WESKAMP and I. COTLIER, Arch. de oftal. de Buenos Aires **15:** 1 (Jan.) 1940.

The authors distinguish with Lindau, Cushing and Bailey two types of angiomas of the central nervous system: (1) tumors cavernous in structure and of reticuloendothelial origin, which they call hemangioblastomas and which are often accompanied with simultaneous retinal tumors of the same type, constituting the Lagleyze, or von Hippel, disease, and (2) tumors in the cerebrum and other parts of the central nervous system and the skin with the structure of benign angiomas (hemangiomas).

They report a case of a cerebral and cutaneous angioma in which there was a retinal lesion which differed ophthalmoscopically from that of the Lagleyze-von Hippel disease and consisted of the dilatation of a retinal vein with numerous arterial miliary aneurysms.

C. E. FINLAY.

TRAUMATIC ANGIOPATHY (PURTSCHER'S DISEASE). V. MUHLMANN and B. VICTORIO RE, Arch. de oftal. de Buenos Aires **15:** 11 (Jan.) 1940.

After a complete clinical description of the disease, a review of 32 cases hitherto reported and reference to 9 others, the authors report an additional case. The patient was a man 38 years of age who two days after receiving a bullet wound in the right sternomastoid region, with lodgment of the bullet in the sixth cervical vertebra, suffered from intense headache and dimness of vision in the right eye.

A preliminary ophthalmoscopic examination showed the fundus of each eye to be normal, but after the onset of the symptoms mentioned numerous white foci and spots irregular in size and shape were observed in the right fundus in the neighborhood of some retinal veins, with a reduction of vision in that eye to 1/8 and concentric contraction of the visual field. There were no retinal hemorrhages. The exudates were mostly absorbed, leaving residual macular hyperemia, reduction of the vision to 1/2, a slight enlargement of the blindspot and a central scotoma for red. The different theories on the pathogenesis of the condition contributed by Purtscher, Vogt, Best, Stähle and Knüssel are discussed.

C. E. FINLAY.

ETIOLOGY OF RETINAL PERIPHLEBITIS. R. SCHMIDT, Arch. f. Ophth. **142:** 1, 1940.

Eight cases of retinal periphlebitis are reported. Active pulmonary tuberculosis of considerable severity was present in 5. In the sixth a tonsil which was removed because of recurrent tonsillitis proved histologically to be the site of a tuberculous process. In the remaining 2 cases death occurred during the period of observation by the ophthalmologist. Although repeated complete physical and roentgenologic examinations had revealed no significant extraocular focus of disease, the autopsies showed severe progressive tuberculosis of intrathoracic lymph glands, with secondary tuberculous involvement of the liver.

In 1 case generalized amyloidosis had developed as a result of the glandular tuberculosis. During the last few months of life the patient's temperature had occasionally been subfebrile, and the sedimentation rate of the blood had been very high.

These two fatal cases illustrate the limitations of clinical methods of examination and confirm Krückmann's view that the intrathoracic glands are the most common source of ocular tuberculosis.

P. C. KRONFELD.

THROMBOANGIITIS (ENDOANGIITIS) OBLITERANS VERSUS TUBERCULOUS RETINAL PERIPHLEBITIS. K. ALBRICH, Arch. f. Ophth. **142:** 286, 1940.

A Hungarian miner aged 40 who had retinal periphlebitis in one eye, with hemorrhages in the vitreous and retinitis proliferans (complicated by acute recurrent iritis), presented the differential diagnostic problem of endoangiitis obliterans versus tuberculous periphlebitis. Marked sensitivity to tuberculin and small calcified pulmonary lesions spoke for tuberculosis, whereas the history (cold hands and feet and healed or compensated thrombosis of a smaller artery of one leg) spoke for endoangiitis obliterans. The patient complained of recurrent lumps in his muscles which were fairly sensitive at first and looked as though they might rupture the overlying skin but finally disappeared completely. At the time of the diagnostic intracutaneous injection of tuberculin one such node happened to be present in one of the arm muscles. Synchronously with the marked local and systemic reaction to the tuberculin the node became markedly larger and very painful. Histologic examination of one such lump showed the picture of endoangiitis obliterans, namely obstruction of the arterial lumen by subendothelial cushion-like granulomas and, consequently, circumscribed necrosis of muscle tissue.

Most authors agree that endoangiitis obliterans occurs in the retina and produces a clinical picture similar to that of tuberculous periphlebitis. On the basis of the ophthalmoscopic observations alone the differentiation between the two diseases is difficult, especially since in the early stages of endoangiitis obliterans the involvement of the veins is more pronounced than that of the arteries. Evanescent nodules in the walls of the veins, which so far have not been reported, would be characteristic of endoangiitis obliterans and not of the tuberculous disease. Endoangiitis obliterans is extremely rare in women (according to Buerger, 3 females among 500 patients), whereas tuberculous periphlebitis occurs four times as often among men as among women. The average age at which endoangiitis obliterans develops is 32. Tuberculous periphlebitis causes its first symptoms at least ten years earlier.

Albrich proposes a new approach to the problem of endoangiitis obliterans versus tuberculous periphlebitis. He suggests that in predisposed persons a tuberculous allergy may produce endoangiitis of the retinal vessels. Later tuberculous bacillemia may lead to lodgment of tubercle bacilli in the retinal vessels sensitized by the previous allergic disease. This concept would furnish an explanation for the various phenomena observed in the case reported.

P. C. KRONFELD.

VASCULAR CHANGES IN A CASE OF TRAUMATIC ANGIOPATHY OF THE RETINA WITH TRANSIENT HYPERTENSION. O. LINDEMAN, Klin. Monatsbl. f. Augenh. **104:** 740 (June) 1940.

A man aged 29 suffered contusion of the right side of the chest, with fracture of ribs, hemoptysis and hemothorax, in an automobile accident. The head was not injured, and the patient did not lose consciousness. On the third day after admission to the hospital the vision was blurred. Both retinas showed edema, numerous fine hemorrhages and white foci in the macula. Striated and dot-shaped hemorrhages could be followed along the arteries into the periphery of the fundus. The veins were greatly narrowed in some places and in other places showed club-shaped distentions presenting the appearance of a string of pearls. The arteries were tortuous and resembled copper wire arteries. Several photographs illustrate the condition which was diagnosed typical traumatic angiopathy of the retina as described by Purtscher. Irregular contraction of the visual fields for white and for colors was present. The blood pressure was 240 mm. of mercury systolic and 160 mm. diastolic on admission and was fairly normal two months later. The cause of the transient hypertension was embolism of a certain area and a sudden increase in blood pressure resulting from compression of the thorax. The ocular condition resulted in bilateral glaucoma. Trephining by Elliot's method failed to normalize the intraocular tension, and vision remained greatly reduced.

K. L. STOLL.

Trachoma

STUDIES ON THE INFECTIVITY OF TRACHOMA. L. A. JULIANELLE, Am. J. Ophth. **23:** 633 (June) 1940.

This is the tenth of a series of articles on trachoma and deals with the frequency and the distribution of the inclusion body and its possible relation to the pathogenesis.

W. S. REESE.

THE TREATMENT OF TRACHOMA WITH SULFANILAMIDE. P. THYGESON, Am. J. Ophth. **23:** 679 (June) 1940.

Thygeson gives the following summary of and conclusions regarding his use of sulfanilamide in the treatment of trachoma:

"In a series of 31 cases of trachoma treated with sulfanilamide, 16 were healed, 11 showed satisfactory improvement, and 4 exhibited little or no change. The drug appeared to be most efficacious in the early cases and when employed in relatively high dosages, but healing was obtained in certain long-standing cicatricial cases and in some in which low doses were given over a relatively long period of time. Sulfanilamide effected rapid disappearance of the epithelial-cell inclusions characteristic of active trachoma, but seemed to have little influence on secondary bacterial infection caused by Haemophilus influenzae, Diplococcus pneumoniae, or Staphylococcus aureus. Corneal lesions responded more rapidly than conjunctival ones, and papillary hypertrophy regressed much more rapidly than follicular hypertrophy."

W. S. REESE.

Uvea

ESSENTIAL PROGRESSIVE ATROPHY OF THE IRIS. J. W. HENDERSON and W. L. BENEDICT, Am. J. Ophth. **23:** 644 (June) 1940.

After reporting a case of atrophy of the iris and presenting a critical review of the literature, Henderson and Benedict give the following summary and conclusions:

"Review of the literature and report of a case of essential progressive atrophy of the iris were made. The literature was studied as regards the qualifications necessary to warrant a diagnosis of essential atrophy of the iris. Eleven cases (or 12, including the case here reported) were found which definitely appear to belong to this group.

"This condition was found to be chiefly a disease of young adults, unilateral in occurrence, more prevalent in females, and ultimately associated with glaucoma. The formation of anterior synechiae, ectropion uveae, and holes in the iris is a frequent accompaniment of this disease.

"Several features of the case reported suggest a mechanical factor as influencing the progression of the atrophy of the iris. No conclusions were made concerning the cause of essential progressive atrophy of the iris.

W. S. REESE.

THREE CASES OF NODULATE IRITIS (IRITIS BOECK?). P. KINDT, Acta ophth. **18:** 38, 1940.

The author describes 3 cases of sluggish iritis occurring in adult women and characterized by the formation of nodules, little pain and a fair tendency toward healing. Provisionally he regards them as being cases of Boeck's sarcoid. The nodules were grayish and semitransparent. They were fairly large, many being visible to the unaided eye. The smaller ones were smooth and round, whereas the larger ones were slightly uneven and somewhat irregular in shape. A few were so prominent as to protrude into the anterior chamber. They showed no tendency to grow into the sclera. They were interlaced and covered on the surface by fine vessels and thus were sharply outlined from the contiguous iris tissue, which appeared normal and without vascularization. Tuberculous nodules are not so sharply outlined, merging gradually into iris tissue which is often vascularized.

O. P. PERKINS.

UVEOPAROTID FEVER IN A CASE OF BOECK'S SARCOID. E. DALSGAARD-NIELSON, Acta ophth. **18:** 210, 1940.

A man of 28 had swelling of both parotid glands, together with bilateral iridocyclitis. Roentgenograms of the lungs showed a considerable enlargement of the hilar shadows on each side, but the bones of the hands and feet showed no characteristic changes. A piece of the parotid gland was excised and revealed changes which were interpreted as those of Boeck's sarcoid. An iridectomy was performed on one eye because of secondary glaucoma, but the iris tissue, which had failed to show nodules clinically, revealed no microscopic changes characteristic of sarcoid. The author believes the case to demonstrate a close relation between uveoparotid fever and benign lymphogranulomatosis.

O. P. PERKINS.

Therapeutics

THE USE OF PYRIFER IN OPHTHALMOLOGY. A. MIKLOS, Arch. f. Ophth. **142:** 58, 1940.

Pyrifer is a proprietary vaccine made from nonpathogenic strains of Escherichia coli (manufactured by Aristopharm, Switzerland). The vaccine is used for the production of artificial pyrexia. The initial dose for healthy adults is 50,000,000 organisms by intravenous injection. The temperature starts to rise two hours later and reaches its maximum (39 to 40 C.; 102 to 104 F.) after another six to eight hours. There is no danger of abscesses at the site of the injection or of anaphylactic shock. The degree and the duration of the pyrexia are more uniform than after intramuscular injections of milk. "In my opinion," the author states, "pyrifer will soon replace all other foreign proteins used for the production of artificial pyrexia."

P. C. KRONFELD.

Society Transactions

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Twelfth Scientific Meeting, Cleveland, June 3, 1941

Studies in Capsular Permeability and Swelling of the Lens. JOHN G. BELLOWS, M.D., PH.D. and HERMAN CHINN, PH.D., Chicago.

Alterations in the permeability of the lens capsule have been postulated as an important factor in the pathogenesis of cataract. Among the methods employed to study this permeability have been experiments in vitro on the swelling capacity of the lens. Such studies afford information on the passage of water through the capsule. The effect of various chemical and physical influences on this passage can then be determined by measuring the relative swelling tendencies. The most extensive studies in which this procedure has been used are those by Fischer, Manca and Ovio and Bottazi and Scalinzi.

The swelling of the lens is greatly affected by the tonicity of the surrounding medium. Normally the lens is bathed by an isotonic solution so that no or only slight changes in its volume result. Thus, when the lenses of cattle were immersed in normal vitreous humor in vitro for periods up to four hours, a change in weight of no more than 1 to 2 per cent was noted. On dilution of the vitreous, the swelling of the lens increased directly with the hypotonicity of the solution and the time of immersion.

A number of organic substances of physiologic interest were tested in iso-osmotic concentrations. Of these, a marked decrease followed the use of dinitrophenol, acetone, acriflavine, quinine and alpha naphthol. This effect by dinitrophenol is significant in view of the consistently negative findings reported thus far on the pathogenesis of this type of cataract. The action of acetone is interesting as a possible influence in the diabetic type of cataract. The other compounds, containing various sugars, hormones, vitamins and drugs, yielded essentially negative results.

Roentgen therapy in doses up to 33,000 r produced no significant disturbance of the swelling properties. Negative results were also obtained with variations of hydrostatic pressure on the lens (5 mm. to 100 mm. of mercury).

Lenses exposed directly to ultraviolet rays showed a diminished swelling owing to coagulation of the more superficial layers. When a thin layer of water covered the lens, exposure resulted in an increased swelling and marked capsular fragility.

Significant changes were rapidly produced by electrical means. The whole eye was exposed to a low frequency current of 100 kilovolts. Exposures from one to ten seconds produced a marked diminution of

the swelling. High voltage associated with high frequency (as generated by a Victor variofrequency diathermy apparatus) had no effect even after a twenty second exposure. Passage of a 110 volt direct current through isotonic saline solution containing the lens decreased slightly the water uptake.

DISCUSSION

DR. JONAS S. FRIEDENWALD, Baltimore: I should like to ask a few questions in relation to some of the phenomena that Dr. Bellows has reported without explanation.

In respect to the effect of various gases on the swelling of the lens, has it occurred to him that those gases which had a depressing effect on the swelling of the lens were the gases which make ions in solution and that, therefore, the tonicity of his solution when he bubbled hydrogen sulfide or carbon dioxide through it was considerably higher than when he bubbled hydrogen or nitrogen?

In the second place, he pointed out the fact that of those ions which exist in two valence forms the one that has the higher valence has the greater effect.

When an ion exists in two valence forms, the one that has the higher valence is an oxidizing substance, and I should like to know whether the greater effect could be correlated with oxidation in view of the fact that the lens protein has readily oxidizable side chains.

DR. JOHN G. BELLOWS, Chicago: Dr. Friedenwald's point as to a higher tonicity having a depressing effect on the swelling is well taken. The gases that produce the decrease, such as hydrogen sulfide and carbon dioxide, would have greater osmotic powers than the others owing to their solubility in the medium. This would certainly tend to lower the swelling of the lens. I doubt whether the ionic concentration would be appreciably affected, since both hydrogen sulfide and carbonic acid are weakly dissociated. We were unable to detect any change in p_H during the bubbling, which indicates that little dissociation had taken place.

The decreased swelling with hydrogen sulfide might be largely accounted for on the basis suggested by Dr. Friedenwald, since this was rather slight. I think it improbable, however, that the marked decrease in swelling with carbon dioxide can be explained to any great extent as a purely osmotic phenomenon. A saturated solution of carbon dioxide would be equivalent to only about a 0.03 molar solution, whereas to produce a comparable decrease in swelling a considerably higher osmotic force would be necessary.

As far as oxidation of the protein and the higher valence is concerned, that is a relation I did not consider at all. Perhaps Dr. Chinn could answer the question.

DR. HERMAN CHINN, Chicago: The increased oxidizing power of the compound with the higher valence might somehow account for a slightly greater swelling of the lens. Is is doubtful, however, that this effect could be very marked. The oxidizing tendency of a system is related to its electrode potential (E_0). The higher the potential the more oxidizing the system. Magnesium has an E_0 of $+ 1.87$, a high value, while the E_0 of tin is only $+ 0.14$. Nevertheless, the swelling of the lens in stannous chloride solution is almost three times that in a

magnesium chloride solution of the same molarity. In general no correlation could be established between the swelling of the lens and the oxidizing ability of the solution. Nor did an increased valence necessarily produce an increased swelling. Thus, the chloride of tetravalent thorium ($ThCl_4$) caused much less swelling than did the chloride of univalent potassium (KCl) or lithium (LiCl).

Relation of Epinephrine to the Secretion of Intraocular Fluid. Dr. Jonas S. Friedenwald and Dr. Wilhelm Buschke, Baltimore.

The present investigation represents a continuation of studies on the secretory activity of the ciliary body which have been reported previously. In summary, these studies have shown that the ciliary processes constitute a secretory organ and that the secretory activity is accomplished through a chemical interaction between the epithelium and the stroma of this organ's tissue. The interaction is an oxidative one, the epithelium oxidizing the stroma. It is made possible by the presence in the epithelium of oxidase enzymes and the presence in the stroma as well as in the epithelium of dehydrogenase enzymes. The two enzyme systems are connected by a set of redox mediators, i. e., substances capable of reversible oxidation and reduction which react serially with one another, forming a chain of oxidative reactions, one end of which is oxidized by the epithelial oxidases while the other end is reduced by the stromal dehydrogenases. Such chains of reactions are the normal pathways of intracellular metabolism and have here for the first time been shown to operate in intercellular metabolism as well.

The experimentally observable phenomena by which this intercellular oxidative chain manifests itself are elicited through the use of various redox indicator dyes in the living or surviving tissue. On the basis of such phenomena it can be shown that animals made deficient in epinephrine by adrenalectomy (with administration of adrenal cortex extract) manifest a temporary complete interruption of the intercellular oxidative interaction in the ciliary body. Associated with this there is a loss of the capacity of the tissue to accumulate various acid and basic dyes unequally in the two tissue components and also a decrease in the capacity of the tissue to regenerate intraocular fluid after puncture of the anterior chamber. Normal activity can be restored by the administration of epinephrine either to the intact animal or to excised surviving tissue fragments. It follows that epinephrine supplies a link in the redox chain of the intercellular metabolism of the ciliary body.

Experimental Transplantation of the Extraocular Muscles in Monkeys. Dr. P. J. Leinfelder and Dr. Nelson M. Black Jr., Iowa City.

Experimental transpositions of the extraocular muscles have been made in monkeys. Interchanging the insertion of the tendon of the medial rectus muscle and that of the inferior rectus muscle results in a return of normal function in approximately three days. If the animal is placed in total darkness immediately after the transplantation operation, there is a slight prolongation of the recovery period but association of rotations, including convergence, is reestablished within a week.

Interchange of the insertion of the tendon of the medial rectus muscle with that of the inferior rectus muscle and of the insertion of the superior rectus muscle with that of the lateral rectus muscle results in a return of associated rotations in six to ten days. When the animal is placed in darkness the recovery period is lengthened to seven to fourteen days. Although the return of associated movements is good, there is some disturbance of coordinated rotations, which consists of a limitation in the extent of rotations and a tendency for the abducted eye to turn slightly upward. This may be the result of mechanical disadvantage dependent on the interchange.

In some animals the tendon of the superior oblique muscle was removed at the time of the transposition of the rectus muscles. This procedure was followed by complete failure of recovery of coordinated associated movements. Animals in the light and in total darkness behaved the same.

It seems impossible to reconcile the return of normal function after transposition of the extraocular muscles with the present theory concerning the supranuclear center controlling associated ocular movements. This theory is that the convergence center in the midbrain sends nerve fibers for convergence to the nucleus of the medial rectus muscle (Perlia's nucleus), where the impulse is transmitted to the medial rectus muscle. After transposition the inferior rectus muscle would be executing convergence, but no known connection exists between the convergence center and that muscle. In a similar manner, the centers for lateral gaze are not connected with the muscles performing this movement after transposition.

The recovery of normal rotations in total darkness appears to indicate that other factors than vision are responsible for maintenance of coordinated ocular rotations. Although available information concerning the presence of proprioceptive fibers in the extraocular muscles is inconclusive, these experiments appear to substantiate their presence.

DISCUSSION

Dr. Conrad Berens, New York: Did you transplant the superior oblique muscle? If so, what was the result? The question is asked because of the surprising return of associated movements, although limited, following transplantation of the superior oblique muscle for third nerve paralysis with ptosis.

Dr. Leinfelder, Iowa City: No, I have not done any operative work on the superior oblique muscle except the resection of the tendon, and I think the experiments do show that there appears to be a profound relationship between coordinated ocular rotations and the superior oblique muscle.

However, much more work is necessary before any definite conclusions can be drawn, and we want to follow this work with graduated operations to see what happens when we operate on two muscles and then on two more and finally resect the superior oblique muscle. This may show what muscles are responsible for maintenance of coordination.

It may be that in doing a three stage operation we can operate on all five of the muscles and retain normal rotations. We shall be much interested to find out whether or not we can.

DR. WALTER B. LANCASTER, Hanover, N. H.: Will Dr. Leinfelder repeat the description of the cat?

DR. P. J. LEINFELDER, Iowa City: I cut the optic nerve and the eighth nerve and removed the cerebellum; the animal became very ugly and lay prone in its cage.

DR. WALTER B. LANCASTER, Hanover, N. H.: I understood Dr. Leinfelder to say that the operation did not affect the ocular rotations.

DR. P. J. LEINFELDER, Iowa City: No, it did not.

DR. WALTER B. LANCASTER, Hanover, N. H.: How were they tested?

DR. P. J. LEINFELDER, Iowa City: We observed spontaneous coordinated rotations.

DR. WALTER B. LANCASTER, Hanover, N. H.: Not random?

DR. P. J. LEINFELDER, Iowa City: They were random but not nystagmoid.

DR. W. H. MARSHALL, Baltimore: What is the possibility that retrograde degeneration has affected the motor nuclei after resection of the superior oblique muscle?

DR. P. J. LEINFELDER, Iowa City: We intend to investigate that, but I do not believe that we need be concerned about degeneration of the motor nuclei, since the physiologic result shows that all the transposed muscles are active. The physiologic result even in the animal with the abnormal rotation is correct for the transpositions that have been made.

DR. WALTER B. LANCASTER, Hanover, N. H.: The matter of orientation interests me particularly. How did you study that in the case of monkeys?

DR. P. J. LEINFELDER, Iowa City: We did not study it any further than the casual observation that when the one animal was freed from the examination box and put into its cage its activity was markedly reduced and inaccurate and that it was always much quieter in the cage than its cage mate. When jumping it would frequently not catch the bars and would fall.

DR. WALTER B. LANCASTER, Hanover, N. H.: How many muscles had to be cut before the orientation was affected?

DR. P. J. LEINFELDER, Iowa City: Five muscles in each eye were operated on.

DR. WALTER B. LANCASTER, Hanover, N. H.: As long as the animals had one eye could they catch the bar?

DR. P. J. LEINFELDER, Iowa City: That is right, but as soon as the second eye was operated on the animals apparently lost all contact with what they were doing.

DR. WALTER B. LANCASTER, Hanover, N. H.: Did the animals show signs of closing the injured eye when they worked with one eye?

DR. P. J. LEINFELDER, Iowa City: Many of the monkeys did at times, but it was surprising that they did not run around the cages with one eye shut. Most of the time they had both eyes open.

DR. JONAS FRIEDENWALD, Baltimore: How much of a twist is produced by the four muscle operation?

DR. P. J. LEINFELDER, Iowa City: I am not sure. We must check this anatomically.

We attempt to minimize twist by crossing opposite pairs of muscles. While we cross the medial and the inferior rectus muscle in one direction, which gives a twist in one direction, we try to neutralize that by crossing the superior and the lateral rectus muscle in the other direction.

I should say offhand that there is not a great amount of twist, but this does have to be checked.

DR. E. SACHS, Detroit: Would it be possible to eliminate proprioceptive impulses from the superior oblique muscle by the use of cocaine?

DR. P. J. LEINFELDER, Iowa City: We have not tried to do so, and I doubt whether this would be of much value.

DR. E. SACHS, Detroit: What do you expect from the diminution of the neck impulses by putting the animals in plaster of paris casts?

DR. P. J. LEINFELDER, Iowa City: I am not sure. Such connections must be considered along with all the oculomotor connections from the vestibular system, the basal ganglions and possibly the cerebellum and those that appear to originate from the superior oblique muscle.

DR. DERRICK VAIL, Cincinnati: How do you explain the lid ptosis?

DR. P. J. LEINFELDER, Iowa City: I interpreted that in part as an attempt to avoid full vision; in other words, a closure of the one eye in order to avoid diplopia. This phenomenon was not present when the animals were free in their cages.

I will say to Dr. Vail that I had not considered it very seriously.

DR. ALEXANDER E. MACDONALD, Toronto, Canada: Do you think that there is a righting reflex mechanism present, primitive or heliotropic, to explain the control of ocular movements after section of the optic nerve and the eighth nerve and removal of the cerebellum?

DR. P. J. LEINFELDER, Iowa City: I do not know. Our experiments are directed toward an explanation of this phenomenon.

Protein Content of the Aqueous Humor in Man. DR. PETER C. KRONFELD, Chicago.

The present knowledge of the protein content of the aqueous humor in the commoner laboratory animals may be summed up as follows: The proteins of the aqueous are specifically identical with those of the blood serum. The absolute quantities of protein in the aqueous of unirritated eyes varies from 14 to 84 mg. per hundred cubic centimeters in the rabbit and from 15 to 55 mg. per hundred cubic centimeters in the cat. This amount is characteristically influenced by diuretics, certain alkaloid and experimental alterations of the sympathetic innervation. Based on these facts is the widely accepted view that the protein concentration in the aqueous depends chiefly on the permeability of the blood-aqueous barrier. A year ago before this association, Swan and Hart presented evidence corroborating this view.

Of the determinations of the protein content of the aqueous in man which are reported in the literature, not more than about 25 can be considered as reasonably accurate. The specimens of aqueous in these 25 instances were obtained from eyes with varying clinical conditions, and the results, which range from 10 to 34 mg. of protein per hundred cubic centimeters of aqueous, were arrived at by different methods. Most of these methods were based on measurements of the turbidity of the aqueous produced by the addition of protein-precipitating reagents (nephelometry). The object of the studies reported herein was to determine whether or not such turbidimetric methods are applicable to the aqueous proteins and what the accuracy of those methods is. These studies led to the detection of a number of factors which influence the result. A method of adequate accuracy for clinical purposes was finally evolved.

The next step was to establish some of the basic facts with regard to the protein content of the aqueous in man, that is the range of physiologic variations in the same or in different persons, the value which constitutes the upper border of normal and the influence of diseases other than local inflammatory ones.

Specimens of aqueous were obtained from three groups of patients, namely: (1) patients whose ocular conditions were such as to make them appear suitable as normal controls, (2) patients with a form of retrobulbar neuritis which is common in China and (3) patients with primary atrophy of the optic nerve.

The range of variations of the protein content was approximately the same in each of these three groups. Repeated determinations of the protein content on the same eye done on patients of groups 2 and 3 at intervals of three weeks showed (1) a high degree of consistency of the protein content in the same eye, (2) no significant differences between aqueous samples obtained by complete and those obtained by incomplete puncture of the anterior chamber and (3) characteristic variations due to the influence of drugs.

In cases of compensated glaucoma the protein content of the aqueous was found to be normal, as reported before by other writers, whereas in cases of senile cataract it was found to be definitely increased.

The Spectral Sensitivities of the Color Receptors as Measured by Dark Adaptation. Dr. Joseph Mandelbaum and Esther U. Mintz, Ph.D., New York.

With dark adaptation as a technic we were able to perform experiments testing whether the classical concept of widely separated sensitivity curves or Hecht's closely overlapping curves are correct. The principle underlying the experiments is that the brighter the bleaching light, the slower the subsequent dark adaptation. The measurements were limited to 1 degree fields in order to include only cones. After bleaching with a "monochromatic" light, dark adaptation measurements were made repeatedly, violet, green and red test lights being used. The speeds of the dark adaptation curves indicated the relative sensitivities of the three receptors—red, green and violet—to the bleaching light.

DISCUSSION

DR. SAMUEL A. TALBOT, Baltimore: Would the essayist discuss Wright's conclusion based on the mixture technic of describing purely chromatic recovery after monochrome adaptation, taking into account the nonlogarithmic law which describes pure chromatic recovery of the brightness threshold? Wright's conclusion was the opposite of that in this essay.

DR. JOSEPH MANDELBAUM, New York: From his data Wright concluded that photochemical regeneration occurs at a uniform rate for each receptor regardless of the adapting intensity (within limits); that there is a "specific effect on each receptor as well as a general depression of sensitivity," and that the data are consistent with his excitation curves, modified slightly. However, at levels of light adaptation above 1,500 photons, "abnormal" effects are produced and the visual processes break down.

Analysis of his data shows that his points, although they appear to lie on straight lines, can nevertheless be described by curves that fit the data as well or better. His extrapolated values for time equals zero lose their significance. It is not surprising that his data should give what appear to be almost straight line functions; this is the inverse of the almost hyperbolic curve which is the customary manner of describing dark adaptation. The sum of the three single recovery curves must equal the total brightness threshold curve (for a brightness match as well as a color match was made). The shape of this function and its dependence on the previous light adaptation have been well established. This is inconsistent with the straight line, uniform recovery rates which he described.

The "abnormal" responses to which he referred, occurring with adapting brightnesses higher than the moderate level of 1,500 photons, are not shown in any data on the various retinal functions which have been studied at photopic levels. He observed that after light adaptation in any spectral region all three retinal processes are markedly affected. This confirms our results. However, he missed entirely the significance of this finding, postulating instead a vague general and specific effect.

The slight transformations he made on his previous excitation curves are based on the assumption that the pure sensations can be matched by spectral colors. This is in conflict with the finding that all spectral colors affect markedly the three responses. His new excitation curves represent the old color mixture data in a slightly modified form, with nothing significant added.

DR. SAMUEL A. TALBOT, Baltimore: Would your adapting lights have enough spectral width to excite widely separated curves?

DR. JOSEPH MANDELBAUM, New York: Our adapting lights were not monochromatic. We used the Eastman kodak, so-called monochromatic filter, series. These gave a considerable range of spectral transmission with maxima that were fairly well defined. The data for the spectral transmission of our filters were given in table 1.

DR. ALBERT C. SNELL, Rochester, N. Y.: Dr. Mandelbaum, would your sensitivity curves be modified in any way by the pigment in the skin; that is by the difference between the fair and the dark complexioned person?

DR. JOSEPH MANDELBAUM, New York: Such a difference would be reflected in color mixture equations and in the photopic visibility curve if it were to appear. As far as I know, no correlation has been found between the pigmentation of the skin and the hair and the photopic visibility curve or color mixture equation.

DR. ALBERT C. SNELL, Rochester, N. Y.: A statement was made by some army investigators to the effect that the Negro race has a greater degree of sensitivity in the dark—a more efficient adaptability—than the white race, and they proposed to employ Negro automobile drivers at night.

DR. JOSEPH MANDELBAUM, New York: I have studied dark adaptation in many patients with a dark complexion but unfortunately never in a Negro. If the Negro light threshold is lower, his visual efficiency under poor illumination would undoubtedly be higher.

DR. G. L. WALLS, Detroit: What was your reason for using stimuli equated in objective intensity rather than in subjective brightness for light adaptation?

DR. JOSEPH MANDELBAUM, New York: The colored filters were calibrated on the Martens photometer by means of heterochromic photometry; the filter factors obtained were used to equate the adapting brightness. Since subjective factors are concerned in heterochromic photometry, our adapting brightness must be considered to be matched subjectively rather than in objective intensity.

Physiologic Studies on Neural Mechanisms of Visual Localization and Discrimination. SAMUEL A. TALBOT, PH.D., AND W. H. MARSHALL, PH.D., Baltimore.

The striate cortex of cats and monkeys gives a sharply localized electric response to restricted flashes of light in the visual field. The main experimental problems are fixation and determination of axis and gaze, preservation of cornea and a sufficiently flexible and intense stimulus, as well as occipital herniation, the type and depth of anesthesia and a rapid way to record buried points.

In both cat and monkey, each hemicortex projects to the contralateral homonymous half-fields of the two eyes, the line of division splitting the fixation point. Within 0.5 degree these fields touch but do not overlap, so that biprojection of the macula does not occur. The vertical meridian on the cat extends for 25 mm. along the dorsal marginal and postmarginal gyri, reaching 40 degrees below and 20 degrees above gaze. Horizontal vision can be followed down the medial wall and laterad on the roof of the splenial sulcus to about 50 degrees from gaze. On the Macacus rhesus monkey brain the vertical meridian courses around the operculum from 7 degrees below gaze at the top to 2.8 degrees above gaze at the bottom. The horizontal meridian extends from the midline, 7.5 degrees lateral from gaze, to a central area about 7 mm. below the opercular tip, which usually has a separate arterial supply. The medial half of this exposed meridian lies approximately over the line where the internal calcarine sulcus meets the inner face of the operculum horizontally. On this internal face the meridian then goes laterally 15 mm. to 11 degrees before turning rostrally.

The resolution of field at 7 degrees from gaze is 20 minutes per millimeter of cortex, but within the 1 degree contour it averages 4 minutes per millimeter of cortex in the monkey. A discontinuity in this slope shows the fovea to project inside a cortical area 6 mm. in radius. The cat's "cortical acuity" is much coarser: near gaze, 1 degree per millimeter, and 30 degrees below gaze, 5 degrees per millimeter.

The anesthetized monkey's energy threshold in central vision for a stimulus area subtending 3 square degrees is about 6 photon seconds, whether in darkness or bright surrounds up to 1 ml. However, at 5 degrees peripherally the threshold stimulus for localized cortical response is twenty-five times lower in dark adaptation than in light. For small short stimuli, threshold strength varies quantitatively with brightness $\times$ area $\times$ time. Consequently the practical stimulus brightness is a limiting factor in reducing stimulus size for precise cortical investigations.

In general, the localized response consists of a primary wave whose latency and amplitude at a cortical point are sensitive to movements of a half-degree stimulus by its own width, and a larger secondary wave about 30 milliseconds later which localizes only very broadly, related possibly to irradiated intraocular light. Peripheral localizations are coarser than central in both cat and monkey. Responses from the two eyes differ in component phases at a given cortical point; excitability cycles recorded at this level show interaction and so convergence.

These results suggest a fixed cortical basis for visual localization down to ordinary two point acuity. The phenomena of line and vernier discrimination require a supplemental neural mechanism, which utilizes the powers of a primary projection brain structure far finer grained than the retina. Paradoxically, the reciprocal overlap of adjacent paths refines vision by a process of channeling and peaking. The fiber pathway is multiplied during projection, which further sharpens the cortical image neurally. The added factors of physiologic nystagmus and the excitability cycles of successive synapses combine to give an adequate neural theory of supradiffraction acuity in terms of path lability within the limits of spacial projection previously demonstrated.

DISCUSSION

DR. G. L. WALLS, Detroit: Need one believe in any multiplication of elements between retina and cortex, considering Clark's recent demonstration of short association fibers covering a 1 cc. circle around each cortical visual cell? There is no evidence that the number of optic radiation fibers exceeds the number of optic tract fibers.

DR. SAMUEL A. TALBOT, Baltimore: The reciprocal overlap produces a functional multiplication of the path at the external geniculate body regardless of the structure relations. However Le Gros Clark has just published direct evidence that the radiation fibers do exceed the optic fibers by at least 5 to 1 in certain layers of the monkey's geniculate body, confirming our indirect conclusion from Cajal.

The argument about resolving power is based more on the amount of overlap, which is supported by the recent evidence of O'Leary on the cat's lateral geniculate body. The dendrite structure of the monkey's radiation cells, shown by Clark, suggests a similar overlap in the primate.

DR. DAVID HARRINGTON, San Fancisco: Does multiplication of the path explain satisfactorily the phenomenon of visual field congruity in calcarine lesions as contrasted with asymmetric fields in the anterior radiation?

DR. SAMUEL A. TALBOT, Baltimore: I do not think I am competent to answer that question, because I do not know enough about the detailed distribution of fibers in the radiation.

DR. H. J. SMITH, Chicago: I should like to ask the speaker if he has any evidence on the asserted overlapping of the crossed and uncrossed fibers in the external geniculate body and their reversal on the opposite side of the brain. I have forgotten who worked out that theory, but I found it in the literature. The fibers from the same geniculate body, the crossed fibers and the uncrossed fibers, were found to locate or terminate in different layers alternately in the external geniculate body; on the opposite side of the brain the exactly reverse order was observed.

Does Dr. Talbot find that to be true? Does he support that belief?

DR. SAMUEL A. TALBOT, Baltimore: Not directly. We have looked for overlapping but we have not been able to demonstrate definitely with electrodes the specific activities of a single geniculate layer. We are still working on this. Layering seems to be supported by a great deal of anatomic evidence. The picture is confirmed physiologically by the relations of facilitation and inhibition between the eyes, at the geniculate level. Would Dr. Marshall care to comment on that?

DR. W. H. MARSHALL, Baltimore: If I understand the proposition, anatomically there is no doubt about the layer structure.

DR. H. J. SMITH, Chicago: Then just one question more. Did the speaker say that in the retinal localization the upper temporal fibers and the upper nasal fibers are of about the same distribution?

DR. SAMUEL A. TALBOT, Baltimore: In both the cat and the monkey the upper temporal fibers from one eye project to the same cortical area as the upper nasal fibers of the other eye.

DR. H. J. SMITH, Chicago: Do you find that the upper and the lower nasal fibers have a corresponding termination in the calcarine area?

DR. SAMUEL A. TALBOT, Baltimore: The upper and the lower nasal fibers from one eye project not to the same but to sagittally adjacent areas on the striate cortex of these animals.

DR. H. J. SMITH, Chicago: Also, in the macula do the essayists find that the fibers terminate toward the internal geniculate body dorsally?

DR. SAMUEL A. TALBOT, Baltimore: The "macular" fibers terminate dorsally on the cat's external geniculate body, according to our functional observations.

Experimental Studies on Detachment of the Vitreous. DR. LUDWIG VON SALLMANN, New York.

Interest in the pathogenesis of detachment of the vitreous has increased since the realization of its causative importance in the development of ruptural detachment of the retina (Leber, Nordenson, Gonin, Lindner and others) and because of the frequency of its occurrence as

a myopic and senile change found by clinical examination (Lindner, Sallmann, Rieger and Fronimopoulos) and by histologic (Lindner) and macroscopic (Sallmann) examination.

The following experiments are related to the most frequent cases of detachment of the vitreous with disinsertion of the vitreous at the disk border, characterized clinically by a ring-shaped opacity in front of and below the nerve head.

In reproducing this condition in vitro by cutting off the nerve head and a piece of the surrounding retina from the vitreous preparations with protected bases, it was found that the vitreous frequently lost volume in a solution of 0.9 per cent sodium chloride in vitreous fluid—in contrast to the swelling usually found in preparations with nerve head and retina in place in similar solutions (Sallmann).

Despite the differences between experimental conditions and those in the living eye, the results of these experiments are applicable to the latter. It is probable that degenerative changes around the disk in myopic and senile eyes extend to the structures of the area martegiani. As in these experiments, the vitreous fluid may leave there in greater amounts, especially if the axial parts of the vitreous are liquefied.

Experiments with hydrating neutral salts in high concentrations show a swelling of the vitreous up to 26 per cent. In preparations without nerve head, however, the expansion is either not demonstrable or is a very small one. It can be concluded therefore that the decrease in the volume of the vitreous caused by a defect at the area martegiani is irreversible.

Shrinkage of the vitreous preparations may be produced in vitro (1) by strongly acid (p_H 3) and alkaline (p_H 11) solutions, (2) in alcohol of more than 40 per cent concentration, (3) in low concentrations of neutral salts (after desalination of the vitreous) and (4) in high concentrations of dehydrating neutral salts following the lyotrope series of anions.

The last method alone was used in vivo in experiments on rabbits. By intravenous injection of 0.2 cc. of a normal solution of potassium sulfate one may produce a partial detachment of the vitreous without tearing the adhesion at the area martegiani and without causing a retinal detachment. Such a partial detachment of the vitreous was found twelve hours after injection and before marked inflammatory reactions of the inner membranes of the eyes had occurred. In later stages the detachment of the vitreous seems to disappear; so the lesion is probably reversible. The results are not, however, entirely convincing, because of the injury to the vitreous occurring during the operative procedure. To avoid this trauma the anion of the dehydrating salts was introduced into the vitreous through the sclera, uvea and retina by iontophoresis. A detachment of the vitreous was not produced with this method. It may be concluded from control experiments that the lowering of intraocular pressure may have been caused by the dehydrating effect of the anion on the vitreous.

Numerous experiments in vitro with proteolytic enzymes yielded contradictory results. It was possible, however, to produce in vivo by the injection of leukocytes in 2 instances a detachment of the vitreous

which can be compared with the results of vaccination of the vitreous with Aspergillus niger by Straub—the only report of a detachment of the vitreous produced experimentally.

Gliomas of the Retina: Histogenesis and Histopathologic Classification. Dr. Edith M. Parkhill and Dr. W. L. Benedict, Rochester, Minn.

Thirty-five gliomas of the retina were divided on a histologic basis according to degree of differentiation of the tumor cells into two types: an extremely undifferentiated retinoblastoma type and a partially differentiated neuroepithelioma type. A third, well differentiated astrocytoma type, which has been reported rarely, was not found in this series.

Rentinoblastomas and neuroepitheliomas seldom if ever arise from the highly specialized rod and cone cells of the retina or from embryonic cell rests, but they arise from previously apparently normal retinal cells which have by a process of differentiation or anaplasia produced tumor cells. The cells from which the tumors arise are probably those with the least specialized function, the glia, or supporting cells, of the retina; hence the term "glioma retinae," first proposed by Virchow, is on the basis of histogenesis applicable to all these tumors. Gliomas are seen arising most often in the inner nuclear layer, where many glial, or supporting, cells, including the cell bodies and nuclei of the fibers of Müller, are found, and next most often in the ganglion cell and the nerve fiber layers, where also the presence of numerous glial cells, or astrocytes, has been constantly demonstrated.

The presence of rosettes in the neuroepithelioma type of tumor is evidence of partial differentiation of the tumor cells and hence of a somewhat lower degree of malignancy. Clinical results confirm this conclusion. Of 16 traced patients whose glioma was of the neuroepithelioma type, 10 (62.5 per cent) had a good result, whereas of 16 whose glioma was of the retinoblastoma type, 2 (12.5 per cent) had a good result.

DISCUSSION

Dr. T. L. Terry, Boston: In the essayists' work on these intraocular neoplasms have they studied specimens of so-called adenoma of the ciliary process?

Dr. Edith M. Parkhill, Rochester, Minn.: This type of tumor did not appear in our series, and I have not had any opportunity to study it.

Dr. T. L. Terry, Boston: The reason for asking this question is that I am interested in how the essayists would classify this neoplasm.

Dr. Edith M. Parkhill, Rochester, Minn.: I do not believe I could answer the question without examining the tumor microscopically, because our classification depends on the histologic appearance and the differentiation of the cells. It would probably be classified as an adenoma or if evidences of dedifferentiation were present as a low grade adenocarcinoma.

Book Reviews

Eye Hazards in Industry: Extent, Cause, and Means of Prevention. By Louis Resnick. Price, $3.50. Pp. 321. New York: Columbia University Press, for the National Society for the Prevention of Blindness, 1941.

Ocular disease and loss of vision due to injury are of concern primarily to the ophthalmic surgeon. When these conditions occur with frequency in such varied pursuits as mining, manufacturing and transportation they become of practical importance to operatives and employers and to social service workers and nurses as well. This volume is the third in a series of publications by the National Society for the Prevention of Blindness, the last having appeared in 1924, and takes into account the changes in the extent, causes and means of prevention of eye hazards in industry which have taken place in the intervening years. In addition, the subject of occupational diseases of the eye, one of increasing importance in industry, has been studied in the light of the most recent experience. The problem of these hazards has been considered with great thoroughness in its statistical, nosologic and hygienic-preventive aspects, there being separate chapters on defective vision, first aid, mechanical guards, process revision, proper lighting, education and administrative supervision. Appendixes of practical value deal with self appraisal for safety of the eyes in industry, industrial poisons as visual hazards and standards of illumination for industrial interiors. There are many useful and instructive illustrations. In a preface Mr. Lewis H. Carris reports with profound sorrow the untimely death of the author early in 1941. Despite a lingering illness, Louis Resnick worked assiduously to finish this volume and completed the manuscript just three days before his death. *"Si monumentum requiris—"*

PERCY FRIDENBERG.

Lecciones clínicas de medicina oftalmologica. By Carlos Charlin C., M.D. Pp. 380, with numerous illustrations. Santiago, Chile: Ediciones Ercilla, 1941.

This book, written by the professor of ophthalmology at the University of Chile, consists of thirty clinical lessons given to undergraduate students of the medical school.

The lectures include different and nonrelated subjects. Two deal with avitaminosis in keratomalacia and two others with hepatic insufficiency in the same disease. Hysterical amaurosis is well described. The clinical characteristics of dental infections as related to ophthalmology are fully treated. There are four lessons on fundus diseases, including arteriosclerosis of the retina, syphilitic arteritis and papilledema. The chapter on arterial cephalic hypertension is interesting. This condition is diagnosed by the application to the sclera of the Bailliart dynamometer (or, better, syphygmoscope). When the maximum retinal pressure is more than double the brachial pressure, the author considers

the former a "limited pathologic cephalic hypertension," and there are the added symptoms of severe headaches, appearance of phosphenes, dizziness, transient paresis, aphasia, etc. Although in some cases there is no general hypertension in the brachial artery, the tibial pressure may be higher than normal.

In another lecture the author considers the entity which he has described for some years by the name "syndrome of the nasal nerve." The patient has violent orbitonasal neuralgia, keratitis and acute rhinitis on the same side as the neuralgia, with a profuse watery discharge. The cause is neuritis of the nasal nerve. He has also found iritis, scleritis and conjunctivitis.

The retinosis of diabetes and that of albuminuria are minutely described. An interesting chapter deals with tuberculosis of the eye and scrofulosis in children and in adults. Treatment with tuberculin is frequently used by the author.

The lectures are written in a conversational, fluent style which vividly reminds one of the old French masters at their hospital clinics. The method is a fascinating way of presenting the subjects to undergraduates, as at the same time that the patient is shown the history and symptoms are clearly and fully described and discussed.

The whole book reflects well the personality of the author and speaks highly of the development of modern ophthalmology in the South American countries.

MANUEL URIBE TRONCOSO, New York.

News and Notes

EDITED BY W. L. BENEDICT

SOCIETY NEWS

North Dakota Academy of Ophthalmology and Otolaryngology.—At a meeting in Fargo on November 29 Dr. A. E. Spear, of Dickinson, was elected president. Dr. Henry P. Wagener, of Rochester, Minn., presented an illustrated address on "Cardiovascular Changes in the Retina."

Directory of Ophthalmologic Societies *

INTERNATIONAL

International Association for Prevention of Blindness

President: Dr. P. Bailliart, 66 Boulevard Saint-Michel, Paris, 6e, France.
Secretary-General: Prof. M. Van Duyse, Université de Gand, Gand, Prov. Ostflandern, Belgium.
All correspondence should be addressed to the Secretariat, 66 Boulevard Saint-Michel, Paris, 6e, France.

International Ophthalmologic Congress

President: Prof. Nordenson, Serafimerlasarettet, Stockholm, Sweden.
Secretary: Dr. Ehlers, Jerbanenegade 41, Copenhagen, Denmark.

International Organization Against Trachoma

President: Dr. A. F. MacCallan, 17 Horseferry Rd., London, England.

Pan-American Congress of Ophthalmology

President: Dr. Harry S. Gradle, 58 E. Washington St., Chicago.
Executive Secretaries: Dr. Conrad Berens, 35 E. 70th St., New York. Dr. M. E. Alvaro, 1511 Consolacao, São Paulo, Brazil.

FOREIGN

All-India Ophthalmological Society

President: Dr. B. K. Narayan Rao, Minto Ophthalmic Hospital, Bangalore.
Secretary: Dr. G. Zachariah, Flitcham, Marshall's Rd., Madras.

British Medical Association, Section on Ophthalmology

President: Dr. W. Clark Souter, 9 Albyn Pl., Aberdeen, Scotland.
Secretary: Dr. Frederick Ridley, 12 Wimpole St., London, W. 1.

Chinese Ophthalmology Society

President: Dr. C. H. Chou, 363 Avenue Haig, Shanghai.
Secretary: Dr. F. S. Tsang, 221 Foochow Rd., Shanghai.

Chinese Ophthalmological Society of Peiping

President: Dr. H. T. Pi, Peiping Union Medical College, Peiping.
Secretary: Dr. C. K. Lin, 180 Hsi-Lo-yen, Chienmeng, Peiping.
Place: Peiping Union Medical College, Peiping. Time: Last Friday of each month.

German Ophthalmological Society

President: Prof. W. Lohlein, Berlin.
Secretary: Prof. E. Engelking, Heidelberg.

Hungarian Ophthalmological Society

President: Prof. H. G. Ditroi, Szeged.
Assistant Secretary: Dr. Stephen de Grosz, University Eye Hospital, Maria ucca 39, Budapest.
All correspondence should be addressed to the Assistant Secretary.

Midland Ophthalmological Society

President: Dr. W. Niccol, 4 College Green, Gloucester, England.
Secretary: Mr. T. Harrison Butler, 61 Newhall St., Birmingham 3, England.
Place: Birmingham and Midland Eye Hospital.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and keep it up to date.

NORTH OF ENGLAND OPHTHALMOLOGICAL SOCIETY

President: Dr. A. MacRae, 6 Jesmond Rd., Newcastle-upon-Tyne, England.
Secretary: Dr. Percival J. Hay, 350 Glossop Rd., Sheffield 10, England.
Place: Manchester, Bradford, Leeds, Newcastle-upon-Tyne, Liverpool and Sheffield, in rotation. Time: October to April.

OPHTHALMOLOGICAL SOCIETY OF AUSTRALIA

President: Dr. A. James Flynn, 135 Macquarie St., Sydney.
Secretary: Dr. D. Williams, 193 Macquarie St., Sydney.

OPHTHALMOLOGICAL SOCIETY OF EGYPT

President: Prof. Dr. Mohammed Mahfouz Bey, Government Hospital, Alexandria.
Secretary: Dr. Mohammed Khalil, 4 Baehler St., Cairo.
All correspondence should be addressed to the secretary, Dr. Mohammed Khalil.

OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

President: Mr. T. Harrison Butler, 61 Newhall St., Birmingham 3, England.
Secretary: Mr. L. H. Savin, 7 Queen St., London, W. 1, England.

OPHTHALMOLOGY SOCIETY OF BOMBAY

President: Dr. D. D. Sathaye, 127 Girgaum Rd., Bombay 4, India.
Secretary: Dr. H. D. Dastur, Dadar, Bombay 14, India.
Place: H. B. A. Free Ophthalmic Hospital, Parel, Bombay 12. Time: First Friday of every month.

OXFORD OPHTHALMOLOGICAL CONGRESS

Master: Dr. Percival J. Hay, 350 Glossop Rd., Sheffield 10, England.
Secretary-Treasurer: Dr. F. A. Anderson, 12 St. John's Hill, Shrewsbury, England.

PALESTINE OPHTHALMOLOGICAL SOCIETY

President: Dr. Arieh Feigenbaum, Abyssinian St. 15, Jerusalem.
Secretary: Dr. E. Sinai, Tel Aviv.

POLISH OPHTHALMOLOGICAL SOCIETY

President: Dr. W. Kapuściński, 2 Waly Batorego, Poznań.
Secretary: Dr. J. Sobański, Lindley'a 4, Warsaw.
Place: Lindley'a 4, Warsaw.

ROYAL SOCIETY OF MEDICINE, SECTION OF OPHTHALMOLOGY

President: Dr. A. J. Ballantyne, 11 Sandyford Pl., Glasgow, C. 3, Scotland.
Secretary: Dr. C. Dee Shapland, 15 Devonshire Pl., London, W. 1, England.

SÃO PAULO SOCIETY OF OPHTHALMOLOGY

President: Dr. Jacques Tupinambo, São Paulo, Brazil.
Secretary: Dr. Silvio de Almeida Toledo, Enfermaria Santa Luzia, Santa Casa de Misericordia, Cezario Motta St.—112, São Paulo, Brazil.

SOCIEDAD OFTALMOLOGIA DEL LITORAL, ROSARIO (ARGENTINA)

President: Prof. Dr. Carlos Weskamp, Laprida 1159, Rosario.
Secretary: Dr. Juan M. Vila Ortiz, Córdoba 1433, Rosario.
Place: Rosario. Time: Last Saturday of every month, April to November, inclusive.
All correspondence should be addressed to the President.

SOCIEDADE DE OPHTHALMOLOGIA E OTO RHINO-LARYNGOLOGIA DA BAHIA

President: Dr. Francisco Ferreira, Pitangueiras 15, Brotas, S. Salvador, Brazil.
Secretary: Dr. Adroaldo de Alencar, Brazil.
All correspondence should be addressed to the President.

SOCIETÀ OFTALMOLOGICA ITALIANA

President: Prof. Dott. Giuseppe Ovio, Ophthalmological Clinic, University of Rome, Rome.
Secretary: Prof. Dott. Epimaco Leonardi, Via del Gianicolo, 1, Rome.

SOCIÉTÉ FRANÇAISE D'OPHTALMOLOGIE

Secretary: Dr. René Onfray, 6 Avenue de la Motte Picquet, Paris, 7e.

SOCIETY OF SWEDISH OPHTHALMOLOGISTS

President: Prof. K. G. Ploman, Stockholm.
Secretary: Dr. K. O. Granström, Södermalmstorg 4 Ill tr., Stockholm, Sö.

TEL AVIV OPHTHALMOLOGICAL SOCIETY

President: Dr. D. Arieh-Friedman, 96 Allenby St., Tel Aviv, Palestine.
Secretary: Dr. Sadger Max, 9 Bialik St., Tel Aviv, Palestine.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON OPHTHALMOLOGY

Chairman: Dr. Lawrence T. Post, 508 N. Grand Blvd., St. Louis, Mo.
Secretary: Dr. Derrick Vail, 441 Vine St., Cincinnati.
Place: Atlantic City. Time: June 8-12, 1942.

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY, SECTION ON OPHTHALMOLOGY

President: Dr. Frank R. Spencer, Physicians' Bldg., Boulder, Colo.
President-Elect: Dr. Ralph I. Lloyd, 14–8th Ave., Brooklyn.
Executive Secretary-Treasurer: Dr. William P. Wherry, 1500 Medical Arts Bldg., Omaha.
Secretary: Dr. G. L. McCormick, 626 S. Central Ave., Marshfield.

AMERICAN OPHTHALMOLOGICAL SOCIETY

President: Dr. Allen Greenwood, 82 Commonwealth Ave., Boston.
Secretary-Treasurer: Dr. Eugene M. Blake, 303 Whitney Ave., New Haven, Conn.

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY, INC.

Chairman: Dr. John Evans, 23 Schermerhorn St., Brooklyn.
Secretary-Treasurer: Dr. C. S. O'Brien, University Hospital, Iowa City.

CANADIAN MEDICAL ASSOCIATION, SECTION ON OPHTHALMOLOGY

President: Dr. Alexander E. MacDonald, 170 St. George St., Toronto.
Secretary-Treasurer: Dr. L. J. Sebert, 170 St. George St., Toronto.

CANADIAN OPHTHALMOLOGICAL SOCIETY

President: Dr. J. Vaillancourt, 46 St. Louis St., Quebec.
Secretary-Treasurer: Dr. Alexander E. MacDonald, 421 Medical Arts Bldg., Toronto.

NATIONAL SOCIETY FOR THE PREVENTION OF BLINDNESS

President: Mr. Mason H. Bigelow, 1790 Broadway, New York.
Secretary: Miss Regina E. Schneider, 1790 Broadway, New York.
Executive Director: Mrs. Eleanor Brown Merrill, 1790 Broadway, New York.

SECTIONAL

ACADEMY OF MEDICINE OF NORTHERN NEW JERSEY, SECTION ON EYE, EAR, NOSE AND THROAT

President: Dr. Charles W. Barkhorn, 223 Roseville Ave., Newark.
Secretary: Dr. William F. McKim, 317 Roseville Ave., Newark.
Place: 91 Lincoln Park South, Newark. Time: 8:45 p. m., second Monday of each month, October to May.

CENTRAL WISCONSIN SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. D. G. Hugo, 130 Main St., Oshkosh.
Secretary: Dr. G. L. McCormick, 626 S. Central Ave., Marshfield.
Place: Land O'Lakes. Time: June 1942.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

President: Dr. William D. Rowland, 84 Commonwealth Ave., Boston.
Secretary-Treasurer: Dr. Trygve Gundersen, 243 Charles St., Boston.
Place: Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston. Time: 8 p. m., third Tuesday of each month from November to April, inclusive.

PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY

President: Dr. Ralph A. Fenton, 1020 S. W. Taylor St., Portland, Ore.
Secretary-Treasurer: Dr. C. Allen Dickey, 450 Sutter St., San Francisco.
Place: Portland, Ore. Time: May 11-14, 1942.

PUGET SOUND ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Spencer S. Howe, 103 E. Holly St., Bellingham, Wash.
Secretary-Treasurer: Dr. Barton E. Peden, 419 Stimson Bldg., Seattle.
Place: Seattle or Tacoma, Wash. Time: Third Tuesday of each month, except June, July and August.

ROCK RIVER VALLEY EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. W. H. Elmer, 321 W. State St., Rockford, Ill.
Secretary-Treasurer: Dr. Harry R. Warner, 321 W. State St., Rockford, Ill.
Place: Rockford, Ill., or Janesville or Beloit, Wis. Time: Third Tuesday of each month from October to April, inclusive.

SAGINAW VALLEY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. M. Kessler, 311 Center Ave., Bay City, Mich.
Secretary-Treasurer: Dr. J. H. Curts, 330 S. Washington Ave., Saginaw, Mich.
Place: Saginaw or Bay City, Mich. Time: Second Tuesday of each month, except July and August.

SIOUX VALLEY EYE AND EAR ACADEMY

President: Dr. J. C. Davis, 1615 Howard St., Omaha.
Secretary-Treasurer: Dr. J. E. Dvorak, 408 Davidson Bldg., Sioux Falls, S. D.

SOUTHERN MEDICAL ASSOCIATION, SECTION ON EYE, EAR, NOSE AND THROAT

Chairman: Dr. L. Chester McHenry, Medical Arts Bldg., Oklahoma City.
Secretary: Dr. J. W. Jervey Jr., 101 Church St., Greenville, S. C.
Place: Richmond, Va. Time: November 1942.

SOUTHWESTERN ACADEMY OF EYE, EAR, NOSE AND THROAT

President: Dr. H. L. Brehmer, 221 W. Central Ave., Albuquerque, N. Mex.
Secretary: Dr. A. E. Cruthirds, 1011 Professional Bldg., Phoenix, Ariz.
Place: Albuquerque, N. Mex. Time: November 1942.

SOUTHWESTERN MICHIGAN TRIOLOGICAL SOCIETY

President: Dr. W. M. Dodge, 716 First National Bank Bldg., Battle Creek.
Secretary-Treasurer: Dr. Kenneth Lowe, 25 W. Michigan Ave., Battle Creek.
Time: Last Thursday of September, October, November, March, April and May.

WESTERN PENNSYLVANIA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. C. H. Bailey, 29 S. Oakland Ave., Sharon.
Secretary-Treasurer: Dr. J. McClure Tyson, Deposit Nat'l Bank Bldg., DuBois.

STATE

ARKANSAS STATE MEDICAL SOCIETY, EYE, EAR, NOSE AND THROAT SECTION

President: Dr. R. R. Kirkpatrick, 6th and Walnut Sts., Texarkana, Ark.
Secretary-Treasurer: Dr. Raymond C. Cook, 701 Main St., Little Rock.

COLORADO OPHTHALMOLOGICAL SOCIETY

President: Dr. William M. Bane, 1612 Tremont Pl., Denver.
Secretary: Dr. Harry Shankel, Republic Bldg., Denver.
Place: University Club, Denver. Time: 7:30 p. m., third Saturday of each month, October to May, inclusive.

Connecticut State Medical Society, Section on Eye, Ear, Nose and Throat

President: Dr. Edward N. DeWitt, 836 Myrtle Ave., Bridgeport.
Secretary-Treasurer: Dr. Henry L. Birge, 179 Allyn St., Hartford.

Eye, Ear, Nose and Throat Club of Georgia

President: Dr. E. N. Maner, 247 Bull St., Savannah.
Secretary-Treasurer: Dr. C. K. McLaughlin, 567 Walnut St., Macon.

Indiana Academy of Ophthalmology and Oto-Laryngology

President: Dr. F. McK. Ruby, Union City.
Secretary: Dr. Edwin W. Dyar Jr., 23 E. Ohio St., Indianapolis.
Place: French Lick. Time: First Wednesday in April.

Iowa Academy of Ophthalmology and Oto-Laryngology

President: Dr. J. K. Von Lackum, 117–3d St. S. E., Cedar Rapids.
Secretary-Treasurer: Dr. B. M. Merkel, 604 Locust St., Des Moines.

Louisiana-Mississippi Ophthalmological and Otolaryngological Society

President: Dr. Henry N. Blum, 912 American Bank Bldg., New Orleans.
Secretary-Treasurer: Dr. Edley H. Jones, 1301 Washington St., Vicksburg, Miss.

Michigan State Medical Society, Section of Ophthalmology and Otolaryngology

Chairman: Dr. Robert H. Fraser, 25 W. Michigan Ave., Battle Creek.
Secretary: Dr. R. G. Laird, 114 Fulton St., Grand Rapids.

Minnesota Academy of Ophthalmoloy and Otolaryngology

President: Dr. Erling Wilhelm Hansen, 78 S. 9th St., Minneapolis.
Secretary-Treasurer: Dr. George E. McGeary, 920 Medical Arts Bldg., Minneapolis.
Time: Second Friday of each month from October to May.

Montana Academy of Oto-Ophthalmology

President: Dr. A. L. Hammerel, 208 N. Broadway, Billings.
Secretary: Dr. Fritz D. Hurd, 309 Medical Arts Bldg., Great Falls.

Nebraska Academy of Ophthalmology and Otolaryngology

President: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John Peterson, 1307 N St., Lincoln.

New Jersey State Medical Society, Section on Ophthalmology, Otology and Rhinolaryngology

Chairman: Dr. Edgar P. Cardwell, 47 Central Ave., Newark.
Secretary: Dr. Arthur E. Sherman, 243 S. Harrison St., East Orange.

New York State Medical Society, Eye, Ear, Nose and Throat Section

Chairman: Dr. Searle B. Marlow, 109 S. Warren St., Syracuse.
Secretary: Dr. C. Stewart Nash, 277 Alexander St., Rochester.

North Carolina Eye, Ear, Nose and Throat Society

President: Dr. M. R. Gibson, Professional Bldg., Raleigh.
Secretary: Dr. Vanderbilt F. Couch, 105 W. 4th St., Winston-Salem.

North Dakota Academy of Ophthalmology and Oto-Laryngology

President: Dr. A. E. Spear, Dickinson.
Secretary-Treasurer: Dr. F. L. Wicks, 516–6th St., Valley City.

OREGON ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Paul Bailey, 833 S. W. 11th Ave., Portland.
Secretary-Treasurer: Dr. R. S. Fixott, 1020 S. W. Taylor St., Portland.
Place: Good Samaritan Hospital, Portland. Time: Third Tuesday of each month.

RHODE ISLAND OPHTHALMOLOGICAL AND OTOLOGICAL SOCIETY

Acting President: Dr. N. Darrell Harvey, 112 Waterman St., Providence.
Secretary-Treasurer: Dr. Linley C. Happ, 124 Waterman St., Providence.
Place: Rhode Island Medical Society Library, Providence. Time: 8:30 p. m., second Thursday in October, December, February and April.

SOUTH CAROLINA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. J. L. Sanders, 222 N. Main St., Greenville.
Secretary: Dr. J. H. Stokes, 125 W. Cheves St., Florence.
Place: Columbia. Time: November 1942.

TENNESSEE ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. Wesley Wilkerson, 700 Church St., Nashville.
Secretary-Treasurer: Dr. W. D. Stinson, 124 Physicians and Surgeons Bldg., Memphis.

TEXAS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. E. L. Goar, 1300 Walker Ave., Houston.
Secretary: Dr. Dan Brannin, 929 Medical Arts Bldg., Dallas.

UTAH OPHTHALMOLOGICAL SOCIETY

President: Dr. Everett B. Muir, Boston Bldg., Salt Lake City.
Secretary-Treasurer: Dr. Earl H. Phillips, 623 Judge Bldg., Salt Lake City.
Place: University Club, Salt Lake City. Time: 7:00 p. m., third Monday of each month.

VIRGINIA SOCIETY OF OTO-LARYNGOLOGY AND OPHTHALMOLOGY

President: Dr. Mortimer H. Williams, 30½ Franklin Rd. S. W., Roanoke.
Secretary-Treasurer: Dr. Meade Edmunds, 34 Franklin St., Petersburg.

WEST VIRGINIA STATE MEDICAL ASSOCIATION, EYE, EAR, NOSE AND THROAT SECTION

President: Dr. George Traugh, 309 Cleveland Ave., Fairmont.
Secretary: Dr. Welch England, 621½ Market St., Parkersburg.

LOCAL

AKRON ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. George E. Black, 7 W. Bowery St., Akron, Ohio.
Secretary-Treasurer: Dr. C. R. Andersen, 106 S. Main St., Akron, Ohio.
Time: First Monday in January, March, May and November.

ATLANTA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Stacy C. Howell, 144 Ponce de Leon Ave. N. E., Atlanta, Ga.
Secretary: Dr. Lester A. Brown, 478 Peachtree St. N. E., Atlanta, Ga.
Place: Grady Hospital. Time: 6:00 p. m., second Wednesday of each month from October to May.

BALTIMORE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY

Chairman: Dr. Ernst Bodenheimer, 1212 Eutaw Pl., Baltimore.
Secretary: Dr. Thomas R. O'Rourk, 104 W. Madison St., Baltimore.
Place: Medical and Chirurgical Faculty, 1211 Cathedral St. Time: 8:30 p. m. fourth Thursday of each month from October to March.

Birmingham Eye, Ear, Nose and Throat Club

President: Each member, in alphabetical order.
Secretary: Dr. Luther E. Wilson, 919 Woodward Bldg., Birmingham, Ala.
Place: Tutwiler Hotel. Time: 6:30 p. m., second Tuesday of each month, September to May, inclusive.

Brooklyn Ophthalmological Society

President: Dr. Maurice Wieselthier, 1322 Union St., Brooklyn.
Secretary-Treasurer: Dr. Harold F. Schilback, 142 Joralemon St., Brooklyn.
Place: Kings County Medical Society Bldg., 1313 Bedford Ave. Time: Third Thursday in February, April, May, October and December.

Buffalo Ophthalmologic Club

President: Dr. Meyer H. Riwchun, 367 Linwood Ave., Buffalo.
Secretary-Treasurer: Dr. Sheldon B. Freeman, 196 Linwood Ave., Buffalo.
Time: Second Thursday of each month.

Chattanooga Society of Ophthalmology and Otolaryngology

President: Each member, in alphabetical order.
Secretary: Dr. Douglas Chamberlain, Chattanooga Bank Bldg., Chattanooga, Tenn.
Place: Mountain City Club. Time: Second Thursday of each month from September to May.

Chicago Ophthalmological Society

President: Dr. Sanford Gifford, 720 N. Michigan Ave., Chicago.
Secretary-Treasurer: Dr. Vernon M. Leech, 55 E. Washington St., Chicago.
Place: Chicago Towers Club, 505 N. Michigan Ave. Time: Third Monday of each month from October to May.

Cincinnati General Hospital Ophthalmology Staff

Chairman: Dr. D. T. Vail, 441 Vine St., Cincinnati.
Secretary: Dr. A. A. Levin, 441 Vine St., Cincinnati.
Place: Cincinnati General Hospital. Time: 7:45 p. m., third Friday of each month except June, July and August.

Cleveland Ophthalmological Club

Chairman: Dr. W. J. Abbott, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. L. V. Johnson, 2065 Adelbert Rd., Cleveland.
Time: Second Tuesday in October, December, February and April.

College of Physicians, Philadelphia, Section on Ophthalmology

Chairman: Dr. Francis H. Adler, 313 S. 17th St., Philadelphia.
Clerk: Dr. W. S. Reese, 1901 Walnut St., Philadelphia.
Time: Third Thursday of every month from October to April, inclusive.

Columbus Ophthalmological and Oto-Laryngological Society

Chairman: Dr. C. D. Postle, 240 E. State St., Columbus, Ohio.
Secretary-Treasurer: Dr. Hugh C. Thompson, 289 E. State St., Columbus, Ohio.
Place: The Neil House. Time: 6 p. m., first Monday of each month.

Corpus Christi Eye, Ear, Nose and Throat Society

Chairman: Dr. F. K. Stroud, 416 Chaparral St., Corpus Christi, Texas.
Secretary: Dr. Arthur Padilla, 414 Medical Professional Bldg., Corpus Christi, Texas.
Time: Second Friday of each month from October to May.

Dallas Academy of Ophthalmology and Oto-Laryngology

President: Dr. L. A. Nelson, 4105 Live Oak St., Dallas, Texas.
Secretary: Dr. S. F. Harrington, 921 Medical Arts Bldg., Dallas, Texas.
Place: Dallas Athletic Club. Time: 6:30 p. m., first Tuesday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Des Moines Academy of Ophthalmology and Otolaryngology

President: Dr. H. C. Schmitz, 604 Locust St., Des Moines, Iowa.
Secretary-Treasurer: Dr. Byron M. Merkel, 604 Locust St., Des Moines, Iowa.
Time: 7:45 p. m., third Monday of every month from September to May.

Detroit Ophthalmological Club

Chairman: Members rotate alphabetically.
Secretary: Dr. Harvey E. Dowling, 2414 Eaton Tower, Detroit.
Time: 6:30 p. m., first Wednesday of each month.

Detroit Ophthalmological Society

President: Dr. Parker Heath, 1553 Woodward Ave., Detroit.
Secretary: Dr. Leland F. Carter, 1553 Woodward Ave., Detroit.
Place: Club rooms of Wayne County Medical Society. Time: Third Thursday of each month from November to April, inclusive.

Eastern New York Eye, Ear, Nose and Throat Association

President: Dr. James M. Dunn, 1352 Union St., Schenectady.
Secretary-Treasurer: Dr. Joseph L. Holohan, 330 State St., Albany.
Time: Third Wednesday in October, November, March, April, May and June.

Fort Worth Eye, Ear, Nose and Throat Society

President: Dr. W. R. Thompson, 602 W. 10th St., Fort Worth, Texas.
Secretary-Treasurer: Dr. A. E. Jackson, 602 W. 10th St., Fort Worth, Texas.
Place: Medical Hall, Medical Arts Bldg. Time: 7:30 p. m., first Friday of each month except July and August.

Houston Academy of Medicine, Ophthalmological and Oto-Laryngological Section

President: Dr. Wallace W. Ralston, 1304 Walker Ave., Houston, Texas.
Secretary: Dr. William J. Snow, 708 Medical Arts Bldg., Houston, Texas.
Place: Medical Arts Bldg., Harris County Medical Society Rooms. Time: 8 p. m., second Thursday of each month from September to June.

Indianapolis Ophthalmological and Otolaryngological Society

President: Dr. John I. Garret, 57 Stokes Bldg., Indianapolis.
Secretary: Dr. Kenneth L. Craft, 23 E. Ohio St., Indianapolis.
Place: Indianapolis Athletic Club. Time: 6:30 p. m., second Thursday of each month from November to May.

Kansas City Society of Ophthalmology and Oto-Laryngology

President: Dr. Homer Beal, 1103 Grand Ave., Kansas City, Mo.
Secretary: Dr. Desmond Curran, Federal Reserve Bank Bldg., Kansas City, Mo.
Time: Third Thursday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Long Beach Eye, Ear, Nose and Throat Society

Chairman: Dr. Harold Snow, 614 S. Pacific Ave., San Pedro, Calif.
Secretary-Treasurer: Dr. Oliver R. Nees, 508 Times Bldg., Long Beach, Calif.
Place: Professional Bldg. Time: Last Wednesday of each month from October to May.

Los Angeles Society of Ophthalmology and Otolaryngology

President: Dr. John Osburn, 523 W. 6th St., Los Angeles.
Secretary-Treasurer: Dr. Colby Hall, 1136 W. 6th St., Los Angeles.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: 6:00 p. m., fourth Monday of each month from September to May, inclusive.

Louisville Eye and Ear Society

President: Dr. Joseph S. Heitger, Heyburn Bldg., Louisville, Ky.
Secretary-Treasurer: Dr. J. W. Fish, 321 W. Broadway, Louisville, Ky.
Place: Brown Hotel. Time: 6:30 p. m., second Thursday of each month from September to May, inclusive.

Medical Society of the District of Columbia, Section of Ophthalmology and Otolaryngology

Chairman: Dr. E. J. Cummings, 1835 I St. N. W., Washington.
Secretary: Dr. P. S. Constantinople, 1835 I St. N. W., Washington.
Place: 1718 M St. N. W. Time: 8 p. m., third Friday of each month from October to April, inclusive.

Memphis Society of Ophthalmology and Otolaryngology

Chairman: Each member, in alphabetical order.
Secretary: Dr. Sam H. Sanders, 1089 Madison Ave., Memphis, Tenn.
Place: Eye Clinic of Memphis Eye, Ear, Nose and Throat Hospital. Time: 8 p. m., second Tuesday of each month from September to May.

Milwaukee Oto-Ophthalmic Society

President: Dr. John W. Truitt, 161 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. Ralph T. Rank, 238 W. Wisconsin Ave., Milwaukee.
Place: University Club. Time: 6:30 p. m., second Tuesday of each month.

Montgomery County Medical Society

Chairman: Dr. H. V. Dutrow, 1040 Fidelity Medical Bldg., Dayton, Ohio.
Secretary-Treasurer: Dr. Maitland D. Place, 981 Reibold Bldg., Dayton, Ohio.
Place: Van Cleve Hotel. Time: 6:30 p. m., first Tuesday of each month from October to June, inclusive.

Montreal Ophthalmological Society

President: Dr. J. Rosenbaum, 1396 Ste. Catherine St. W., Montreal, Canada.
Secretary: Dr. L. Tessier, 1230 St. Joseph Blvd. E., Montreal, Canada.
Time: Second Thursday of October, December, February and April.

Nashville Academy of Ophthalmology and Otolaryngology

Chairman: Dr. Andrew Hollabaugh, Doctors Bldg., Nashville, Tenn.
Secretary: Dr. Guy Maness, Medical Arts Bldg., Nashville, Tenn.
Place: St. Thomas Hospital. Time: 8 p. m., third Monday of each month from October to May.

New Haven Ophthalmological Society

President: Dr. William H. Ryder, 185 Church St., New Haven, Conn.
Secretary: Dr. Frederick A. Wies, 255 Bradley St., New Haven, Conn.

New Orleans Ophthalmological and Otolaryngological Society

President: Dr. W. B. Clark, 1012 American Bank Bldg., New Orleans.
Secretary: Dr. Mercer G. Lynch, 1018 Maison Blanche Bldg., New Orleans.
Place: Louisiana State University Medical Bldg. Time: 8 p. m., second Tuesday of each month from October to May.

New York Academy of Medicine, Section of Ophthalmology

Chairman: Dr. Kaufman Schlivek, 1016–5th Ave., New York.
Secretary: Dr. Brittain Payne, 896 Madison Ave., New York.
Time: 8:30 p. m., third Monday of every month from October to May, inclusive.

NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

President: Dr. James W. Smith, 1016–5th Ave., New York.
Secretary: Dr. Benjamin Esterman, 983 Park Ave., New York.
Place: Squibb Hall, 745–5th Ave. Time: 8 p. m., first Monday of each month from October to May, inclusive.

OKLAHOMA CITY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. R. E. Leatherock, Cushing, Okla.
Secretary: Dr. Harry C. Ford, 1014 Medical Arts Bldg., Oklahoma City.
Place: University Hospital. Time: Second Tuesday of each month from September to May.

OMAHA AND COUNCIL BLUFFS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. Harold Gifford, 1620 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Place: Omaha Club, 20th and Douglas Sts., Omaha. Time: 6 p. m., dinner; 7 p. m., program; third Wednesday of each month from October to May.

PASSAIC-BERGEN OPHTHALMOLOGICAL CLUB

President: Dr. L. Markowitz, 16 Church St., Paterson, N. J.
Secretary-Treasurer: Dr. A. John Reinhorn, 302 Broadway, Paterson, N. J.
Place: Paterson Eye and Ear Infirmary. Time: 9 p. m., last Friday of every month, except June, July and August.

PHILADELPHIA COUNTY MEDICAL SOCIETY, EYE SECTION

Chairman: Dr. Edmund B. Spaeth, 1930 Chestnut St., Philadelphia.
Secretary: Dr. Wilfred E. Fry, 1819 Chestnut St., Philadelphia.
Time: First Thursday of each month from October to May.

PITTSBURGH OPHTHALMOLOGICAL SOCIETY

President: Dr. J. Clyde Markel, 200–9th St., Pittsburgh.
Secretary: Dr. George H. Shuman, 351–5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine Bldg. Time: Fourth Monday of each month, except June, July, August and September.

READING EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. James E. Landis, 232 N. 6th St., Reading, Pa.
Secretary: Dr. Paul C. Craig, 232 N. 5th St., Reading, Pa.
Place: Wyomissing Club. Time: 6:30 p. m., third Wednesday of each month from October to July.

RICHMOND OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. W. F. Bryce, Medical Arts Bldg., Richmond, Va.
Secretary: Dr. Richard W. Vaughan, Medical Arts Bldg., Richmond, Va.
Place: Westmoreland Club. Time: 6 p. m., second Monday of each month from October to May.

ROCHESTER EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. E. J. Avery, 11 N. Goodman St., Rochester, N. Y.
Secretary-Treasurer: Dr. Charles T. Sullivan, 277 Alexander St., Rochester, N. Y.

ST. LOUIS OPHTHALMIC SOCIETY

President: Dr. William M. James, 508 N. Grand Blvd., St. Louis.
Secretary: Dr. H. Rommel Hildreth, 823 Metropolitan Bldg., St. Louis.
Place: Oscar Johnson Institute. Time: Clinical meeting 5:30 p. m., dinner and scientific meeting 6:30 p. m., fourth Friday of each month from October to April, inclusive, except December.

San Antonio Ophthalmo-Oto-Laryngological Society

President: Dr. Dan Russell, 705 E. Houston St., San Antonio, Texas.
Secretary-Treasurer: Dr. P. G. Bowen, 315 Camden St., San Antonio, Texas.
Place: Bexar County Medical Library. Time: 8 p. m., first Tuesday of each month from October to May.

San Francisco County Medical Society, Section on Eye, Ear, Nose and Throat

Chairman: Dr. Fred Boyle, 490 Post St., San Francisco.
Secretary: Dr. Frank Hand, 450 Sutter St., San Francisco.
Place: Society's Bldg., 2180 Washington St., San Francisco. Time: Fourth Tuesday of every month except June, July and December.

Shreveport Eye, Ear, Nose and Throat Society

President: Dr. David C. Swearingen, Slattery Bldg., Shreveport, La.
Secretary-Treasurer: Dr. Kenneth Jones, Medical Arts Bldg., Shreveport, La.
Place: Shreveport Charity Hospital. Time: 7:30 p. m., first Monday of every month except July, August and September.

Spokane Academy of Ophthalmology and Oto-Laryngology

President: Dr. Louis A. Parsell, 407 Riverside Ave., Spokane, Wash.
Secretary: Dr. Robert L. Pohl, 407 Riverside Ave., Spokane, Wash.
Place: Paulsen Medical and Dental Library. Time: 8 p. m., fourth Tuesday of each month except June, July and August.

Syracuse Eye, Ear, Nose and Throat Society

President: Dr. Roy Seeley Moore, 1704 State Tower Bldg., Syracuse, N. Y.
Secretary-Treasurer: Dr. I. H. Blaisdell, 713 E. Genesee St., Syracuse, N. Y.
Place: University Club. Time: First Tuesday of each month except June, July and August.

Toledo Eye, Ear, Nose and Throat Society

Chairman: Dr. J. E. Minns, 316 Michigan St., Toledo, Ohio.
Secretary: Dr. John D. Skow, 2001 Collingwood Blvd., Toledo, Ohio.
Place: Toledo Club. Time: Each month except June, July and August.

Toronto Academy of Medicine, Section of Ophthalmology

Chairman: Dr. W. R. F. Luke, 316 Medical Arts Bldg., Toronto, Canada.
Secretary: Dr. W. T. Gratton, 216 Medical Arts Bldg., Toronto, Canada.
Place: Academy of Medicine, 13 Queens Park. Time: First Monday of each month, November to April.

Washington, D. C., Ophthalmological Society

President: Dr. E. Leonard Goodman, 1801 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. Sterling Bockoven, 1752 Massachusetts Ave. N. W., Washington, D. C.
Place: Episcopal Eye, Ear and Throat Hospital. Time: 7:30 p. m., first Monday in November, January, March and April.

Wilkes-Barre Ophthalmological Society

Chairman: Each member in turn.
Secretary: Dr. Samuel T. Buckman, 70 S. Franklin St., Wilkes-Barre, Pa.
Place: Office of chairman. Time: Last Tuesday of each month from October to May.